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**Background:** States vary widely in their use of newborn screening tests, with some mandating screening for as few as three conditions and others mandating as many as 43 conditions, including varying numbers of the 40+ conditions that can be detected by tandem mass spectrometry (MS/MS). There has been no national guidance on the best candidate conditions for newborn screening since the National Academy of Sciences report of 1975[1] and the United States Congress Office of Technology Assessment report of 1988,[2] despite rapid developments since then in genetics, in screening technologies, and in some treatments. **Objectives:** In 2002, the Maternal and Child Health Bureau (MCHB) of the Health Resources and Services Administration (HRSA) of the United States Department of Health and Human Services (DHHS) commissioned the American College of Medical Genetics (ACMG) to:

1. Conduct an analysis of the scientific literature on the effectiveness of newborn screening.
2. Gather expert opinion to delineate the best evidence for screening for specified conditions and develop recommendations focused on newborn screening, including but not limited to the development of a uniform condition panel.
3. Consider other components of the newborn screening system that are critical to achieving the expected outcomes in those screened.

**Methods:** A group of experts in various areas of subspecialty medicine and primary care, health policy, law, public health, and consumers worked with a steering committee and several expert work groups, using a two-tiered approach to assess and rank conditions. A first step was developing a set of principles to guide the analysis. This was followed by developing criteria by which conditions could be evaluated, and then identifying the conditions to be evaluated. A large and broadly representative group of experts was asked to provide their opinions on the extent to which particular conditions met the selected criteria, relying on supporting evidence and references from the scientific literature. The criteria were distributed among three main categories for each condition:

1. The availability and characteristics of the screening test;
2. The availability and complexity of diagnostic services; and
3. The availability and efficacy of treatments related to the conditions. A survey process utilizing a data collection instrument was used to gather expert opinion on the conditions in the first tier of the assessment. The data collection format and survey provided the opportunity to quantify expert opinion and to obtain the views of a diverse set of interest groups (necessary due to the subjective nature of some of the criteria). Statistical analysis of data produced a score for each condition, which determined its ranking and initial placement in one of three categories (high scoring, moderately scoring, or low scoring/absence of a newborn screening test). In the second tier of these analyses, the evidence base related to each condition was assessed in depth (e.g., via systematic reviews of reference lists including MedLine, PubMed and others; books; Internet searches; professional guidelines; clinical evidence; and cost/economic evidence and modeling). The fact sheets reflecting these analyses were evaluated by at least two acknowledged experts for

*[†] A medical food is prescribed by a physician when a patient has special nutrient needs in order to manage a disease or health condition, and the patient is under the physician's ongoing care. The label must clearly state that the product is intended to be used to manage a specific medical disorder or condition. An example of a medical food is a food for use by persons with PKU, i.e., foods formulated to be free of the amino acid phenylalanine.*

*[2] The Health Insurance Portability and Accountability Act of 1996 (HIPAA) provides relevant protections regarding patient privacy. The federal privacy regulations do not prohibit or interfere with newborn screening and follow-up. Covered entities must track disclosures made without written patient authorization for services other than treatment, payment, and operations, so that the covered entity can provide accounting on patient request. A discussion of the HIPAA issues relating to newborn screening in the context of public health is available in Appendix 4.*

*[3] This and the following economic analyses may best be done through the funding of special projects due to the expense of documentation*

*[4] Consider collecting data from a subset that includes all screen-positive newborns from which an overall rate can be extrapolated with minimal increased cost to the program. Consider initially collecting data from a subset that includes all screen-positive newborns for which the data already is needed. From these, an overall rate can be extrapolated with minimal increased cost. The goal is to know all and is dependant on the development of databases in which this information can be maintained and would be facilitated by inclusion on blood collection cards. Identification of undocumented newborns is increasingly important to their participation in such programs. This is an important issue that involves States, hospitals, providers, insurers, and mothers.*

*[5] For a guidance article on the HIPAA Privacy Rule and Public Health written by CDC and DHHS. see the Morbidity and Mortality Weekly Report for April 11, 2003, vol. 52 pp. 1-21, and www.cdc.gov/privacyrules and www.hrsa.gov/website.htm.*

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each condition. These experts assessed the data and the associated references related to each criterion and provided corrections where appropriate, assigned a value to the level of evidence and the quality of the studies that established the evidence base, and determined whether there were significant variances from the survey data. Survey results were subsequently realigned with the evidence obtained from the scientific literature during the second-tier analysis for all objective criteria, based on input from at least three acknowledged experts in each condition. The information from these two tiers of assessment was then considered with regard to the overriding principles and other technology or condition-specific recommendations. On the basis of this information, conditions were assigned to one of three categories as described above:

1. Core Panel;
2. Secondary Targets (conditions that are part of the differential diagnosis of a core panel condition.); and
3. Not Appropriate for Newborn Screening (either no newborn screening test is available or there is poor performance with regard to multiple other evaluation criteria).

ACMG also considered features of optimal newborn screening programs beyond the tests themselves by assessing the degree to which programs met certain goals (e.g., availability of educational programs, proportions of newborns screened and followed up). Assessments were based on the input of experts serving in various capacities in newborn screening programs and on 2002 data provided by the programs of the National Newborn Screening and Genetics Resource Center (NNSGRC). In addition, a brief cost-effectiveness assessment of newborn screening was conducted.

**Results:**

**Uniform panel** – A total of 292 individuals determined to be generally representative of the regional distribution of the United States population and of areas of expertise or involvement in newborn screening provided a total of 3,949 evaluations of 84 conditions. For each condition, the responses of at least three experts in that condition were compared with those of all respondents for that condition and found to be consistent. A score of 1,200 on the data collection instrument provided a logical separation point between high scoring conditions (1,200– 1,799 of a possible 2,100) and low scoring ($<$1,000) conditions. A group of conditions with intermediate scores (1,000–1,199) was identified, all of which were part of the differential diagnosis of a high scoring condition or apparent in the result of the multiplex assay. Some are identified by screening laboratories and others by diagnostic laboratories. This group was designated as a "secondary target" category for which the program must report the diagnostic result.

Using the validated evidence base and expert opinion, each condition that had previously been assigned to a category based on scores gathered through the data collection instrument was reconsidered. Again, the factors taken into consideration were: 1) available scientific evidence; 2) availability of a screening test; 3) presence of an efficacious treatment; 4) adequate understanding of the natural history of the condition; and 5) whether the condition was either part of the differential diagnosis of another condition or whether the screening test results related to a clinically significant condition.

The conditions were then assigned to one of three categories as previously described (core panel, secondary targets, or not appropriate for Newborn Screening).

Among the 29 conditions assigned to the core panel are three hemoglobinopathies associated with a Hb/S allele, six amino acidurias, five disorders of fatty oxidation, nine organic acidurias, and six unrelated conditions (congenital hypothyroidism (CH), biotinidase deficiency (BIOT), congenital adrenal hyperplasia (CAH), classical galactosemia (GALT), hearing loss (HEAR) and cystic fibrosis (CF)). Twenty-three of the 29 conditions in the core panel are identified with multiplex technologies such as tandem mass spectrometry (MS/MS) or high pressure liquid chromatography (HPLC). On the basis of the evidence, six of the 35 conditions initially placed in the core panel were moved into the secondary target category, which expanded to 25 conditions. Test results not associated with potential disease in the infant (e.g., carriers) were also placed in the secondary target category. When newborn screening laboratory results definitively establish carrier status, the result should be made available to the health care professional community and families.

Twenty-seven conditions were determined to be inappropriate for newborn screening at this time.

Conditions with limited evidence reported in the scientific literature were more difficult to evaluate, quantify and place in one of the three categories. In addition, many conditions were found to occur in multiple forms distinguished by age-of-onset, severity, or other features. Further, unless a condition was already included in newborn screening programs, there was a potential for bias in the information related to some criteria. In such circumstances, the quality of the studies underlying the data such as expert opinion that considered case reports and reasoning from first principles determined the placement of the conditions into particular categories.

**Newborn screening program optimization** – Assessment of the activities of newborn screening programs, based on program reports, was done for the six program components: education; screening; follow-up; diagnostic confirmation; management; and program evaluation. Considerable variation was found between programs with regard to whether particular aspects (e.g., prenatal education program availability, tracking of specimen collection and delivery) were included and the degree to which they are provided. Newborn screening program evaluation systems also were assessed in order to determine their adequacy and uniformity with the goal being to improve interprogram evaluation and comparison to ensure that the expected outcomes from having been identified in screening are realized. **Conclusions:** The state of the published evidence in the fast-moving worlds of newborn screening and medical genetics has not kept up with the implementation of new technologies, thus requiring the considerable use of expert opinion to develop recommendations about a core panel of conditions for newborn screening. Twenty-nine conditions were identified as primary targets for screening from which all components of the newborn screening system should be maximized. An additional 25 conditions were listed that could be identified in the course of screening for core panel conditions. Programs are obligated to establish a diagnosis and communicate the result to the health care provider and family. It is recognized that screening may not have been maximized for the detection of these secondary conditions but that some proportion of such cases may be found among those screened for core panel conditions. With additional screening, greater training of primary care health care professionals and subspecialists will be needed, as will the development of an infrastructure for appropriate follow-up and management throughout the lives of children who have been identified as having one of these rare conditions. Recommended actions to overcome barriers to an optimal newborn screening system include:

- The establishment of a national role in the scientific evaluation of conditions and the technologies by which they are screened;
- Standardization of case definitions and reporting procedures;
- Enhanced oversight of hospital-based screening activities;
- Long-term data collection and surveillance; and
- Consideration of the financial needs of programs to allow them to deliver the appropriate services to the screened population. ***Genet Med* 2006:8(5, Supplement):12S–252S.**

## INTRODUCTION

The work reported here is pursuant to the HRSA/MCHB Contract No. 240-01-0038, *Standardization of Outcomes and Guidelines for State Newborn Screening Programs*. In 1999, the American Academy of Pediatrics (AAP) Newborn Screening Task Force recommended that, "HRSA should engage in a national process involving government, professionals, and consumers to advance the recommendations of this Task Force and assist in the development and implementation of nationally recognized newborn screening system standards and policies." The Task Force was concerned about the lack of uniformity among states, particularly with regard to their newborn screening condition panels.

In 2001, in response to that recommendation, HRSA/MCHB requested that ACMG outline a process of standardization of outcomes and guidelines for State newborn screening programs and define responsibilities for collecting and evaluating outcome data, including a recommended uniform panel of conditions to include in State newborn screening programs. It was expected that the analytical endeavor and subsequent recommendations be definitive and that the recommendations be based on the best scientific evidence and analysis of that evidence. ACMG was specifically asked to develop recommendations to address:

1. A uniform condition panel (including implementation methodology);
2. Model policies and procedures for State newborn screening programs (with consideration of a national model);
3. Model minimum standards for State newborn screening programs (with consideration of national oversight);
4. A model decision matrix for consideration of State newborn screening program expansion; and
5. Consideration of the value of a national process for quality assurance and oversight.

This report is a product of the work undertaken by ACMG for HRSA. A methods section begins by providing the broad context for the newborn screening system and the overarching principles for developing newborn screening guidelines. It then provides the criteria that were used in the analyses of conditions under consideration for newborn screening programs. This is followed by a description of the development and use of tools to collect data that would complement evidence gathered from a review of the scientific literature, and also by a description of the process for obtaining additional expert information and opinion. The results of these analyses are provided, as well as recommendations for moving forward.

Although the criteria by which the conditions are evaluated and the results of those evaluations are the primary goals of this effort, associated and supporting goals also are described because of their relevance to the newborn screening system. In order to realize the expected outcomes for newborns and their families, the full system must be operating efficiently and effectively.[3–6] Efforts have been made to assess the newborn screening system based on its component parts, which allows for the development of specific standards for program performance and for an assessment of status of the programs. This assessment also provides the opportunity to determine the extent to which a systematic national approach to quality assessment and assurance is possible.

## SECTION I: DEVELOPING A UNIFORM SCREENING PANEL

### A. Background

In the United States, newborn screening is a highly visible and important State-based public health program[2,7–10] that began over 40 years ago. Since the early 1960s, when Robert Guthrie[11,12] devised a screening test for phenylketonuria (PKU) using a newborn bloodspot dried onto a filter paper card, more than 150 million infants have been screened for a number of genetic and congenital disorders. States and territories mandate newborn screening of all infants born within their jurisdiction for certain treatable disorders that may not otherwise be detected before developmental disability or death occurs. Newborns with these disorders typically appear normal at birth. The testing and follow-up services of newborn screening programs are designed to provide early diagnosis and treatment before significant, irreversible damage occurs. Appropriate compliance with the medical management prescribed can allow most affected newborns to develop normally. The generally acknowledged components of a newborn screening system[4,6,13] include the following:

1. Education of professionals and parents;
2. Screening (specimen collection, submission, and testing);
3. Follow-up of abnormal and unsatisfactory test results;
4. Confirmatory testing and diagnosis;
5. Medical management and periodic outcome evaluation; and
6. System quality assurance, including program evaluation, validity of testing systems, efficiency of follow-up and intervention, and assessments of long-term benefits to individuals, families, and society.

Based on cumulative data from newborn screening programs, reported annually to the HRSA-funded NNSGRC, it is estimated that about 1 in every 800 newborns in the United States—or 5,000 of 4.1 million newborns each year—is born with a potentially severe or lethal condition for which screening and the treatment for the prevention of many or all of the complications of the condition are available. As the model for public health-based population genetic screening, newborn screening is nationally recognized as an essential program that aims to ensure the best outcome for the nation's newborn population.

## NEWBORN SCREENING PROGRAMS: THE CHANGING LANDSCAPE

#### The infrastructure landscape.

In the United States, every State (hereafter, the term "State" will include both States and territorial jurisdictions) presently has a statute or regulation mandating or allowing public health newborn screening. As such, newborn screening is universally available in varying forms to all infants born in the United States, regardless of ability to pay or other familial factors (e.g., ethnicity, area of residence, literacy level, or language). It is important that universal access to this screening and its central public health focus are maintained, while efforts move forward to bring uniformity and equity to State screening efforts.

Since the inception of newborn screening, the conditions screened for and the systems developed for follow-up have varied among States. Due to a dearth of national newborn screening standards (aside from the National Committee for Clinical Laboratory Standards (NCCLS) "Standard on Blood Collection on Filter Paper"), guidance from the HRSA-funded Council of Regional Networks for Genetic Services (CORN) and limited advice from national advisory committees and national medical or public health professional organizations regarding newborn screening policies and conditions to be included in screening mandates, each State independently determines the conditions and screening procedures for its program.

Many States utilize advisory committees and seek input from experts and other State newborn screening laboratories

and private companies in addition to independently reviewing the available scientific evidence before making recommendations for test panels. In some States, decisions about newborn screening are in the hands of the State legislature, which controls the State public health system and its finances. Every State has a statute or regulation that allows or mandates universal newborn screening—sometimes specifying the conditions to be screened, the consent/dissent process, the laboratory, and the laboratory testing procedure to be used. In most cases, decisions about the newborn screening panel are delegated to State health officials, a State board of health, or a genetics or newborn screening advisory committee. Sometimes the decision-making process might involve a combination of agencies, advisory bodies, and policy makers.

Pilot studies usually precede the formal implementation of changes to the newborn screening panels. In addition, the mechanism to expand testing panels, change testing protocols, and fund newborn screening varies among the States, with the basic criteria from the inception of newborn screening being used by many.[14] Due to these factors and a lack of national consensus or guidelines, there is presently a large disparity in screening services available to newborns. For example, at the present time, eight States mandate screening for as few as four conditions, while a number of States screen for as many as 30 conditions (information taken from NNSGRC website www.genes-r-us.uthscsa.edu/nbsdisorders.pdf July 20, 2004). This divergence among States regarding which conditions should be mandated for screening has resulted from several factors, including differences in: 1) the level of resources available (personnel, equipment and service capacity); and 2) interpretations of the available data concerning given conditions (incidence, treatability, impact) and new screening methodologies.[15]

Approaches to calculating the number of conditions included in screening also are variable, with some programs counting hemoglobinopathy screening as a single test and others including it as one of several tests (given the simultaneous ability to detect over 700 variant conditions including SS-disease, SC disease, S$\beta$+-thalassemia, etc.). The expert group concluded that there should be standardization of what constitutes a screened condition. (This issue is discussed in greater detail in the section describing the conditions evaluated.)

It is clear that States must retain strong oversight of mandated screening programs in order to ensure the appropriate delivery of quality screening and ancillary services to the screened population. However, how local ancillary services are to be directly provided within programs is less clear, particularly given the nationwide lack of the specialized medical expertise and laboratory testing that is needed to definitively diagnose many of these rarer inherited genetic conditions. One suggestion to address the maldistribution of needed medical expertise has been through the organization of that expertise at the regional level, as with the newly funded HRSA/MCHB Regional Genetics and Newborn Screening Collaboratives. This effort is supported by the history of regionalization (geographically close) and consolidation (geographically dispersed) of newborn screening laboratory testing services, which has been advantageous for States with low numbers of births. Regional programs have higher numbers of laboratory tests, which results in cost savings and decreased analytical variability.

Another challenge raised by the expansion of newborn screening is the lack of interconnecting relationships between child health professionals and subspecialists, particularly in rural areas—a problem complicated by the diversity of very rare conditions identified by the programs. There are limitations in the local availability of specific expertise for many conditions, and considerable needs exist in the areas of training and education throughout the health care system. Furthermore, improvements in the newborn screening system and the expansion of the number of conditions for which screening is offered have costs, and these costs and the associated benefits seem to accrue independently of the public and private health care delivery systems, which complicates their integration. Many States provide the programs necessary to ensure that screening and diagnosis will occur, but they are limited in their ability to ensure long-term management, including the provision of the necessary long-term treatments and services.

The societal implications of expanding newborn screening also are significant. For example, screening for additional conditions that occur with greater frequency in different ethnic groups could lead to discriminatory practices against individuals as well as the ethnic groups associated with particular disorders. In addition, difficult decisions must be made about the nature of the benefits that might be realized from newborn screening. Historically, screening has focused on conditions for which the improvement in outcome for the infant has been substantial. However, newborn screening could identify many conditions for which the improved outcomes may be more incremental, including disorders that are associated with mental retardation, such as fragile X syndrome, for which early intervention programs can improve long-term cognitive outcomes, but not with the expectation of a normal outcome.[16] Finally, the nature of genetic disease is such that knowledge of its presence can be of value to other family members. Previously, this factor has not been considered by newborn screening programs.

Other considerations arise from private sector testing availability and competition. Often, private laboratories—either commercially- or university-based laboratories—offer an expanded number of conditions screened through the technologies they employ. They may provide contracted services to programs or offer additional screening for conditions not mandated in the program in the State in which the family resides. As a result, some States now mandate that all parents be informed of the availability of additional screening tests. This type of information often is delivered at the last minute and its use may not be supported by hospital staff and medical personnel. However, even though additional screening may be available when initiated by consumers, it is only through State public health that access to newborn screening for ***all*** babies can be assured at the present time.

### The changing technological landscape

Three major technological challenges have occurred over the past few decades with regard to newborn screening. The first is the expansion of knowledge of the causes and treatment of genetic diseases. The second is the rapid expansion of diverse technologies that may be used in screening. The third is the proliferation of tiered testing strategies to enhance the positive predictive value of screening.

The sequencing of the human genome as a public/private partnership has allowed for a better understanding of the genetic bases of many diseases. This fundamental biological knowledge has led to the proliferation of new therapies stemming from intensive research efforts in both the private and public sectors. The pace of Food and Drug Administration (FDA) approval of innovative therapies has quickened. These and other factors are likely to continue to lead to an expanding panel of conditions for which newborn screening may be of benefit.

Simultaneously, there are new technological developments that allow more types of testing at reasonable cost that can be considered for application to universal newborn population screening. Examples include hearing screening, EKG screening for long QT syndrome, acylcarnitine screening, screening with molecular arrays, and screening with immunoaffinity columns. Particularly notable is the implementation of multiplex platforms that allow a single type of specimen preparation and simultaneous (or nearly simultaneous) screening for multiple different disorders. Going from one test for one disorder to one test for multiple disorders has the potential to reduce costs per condition tested and can lead to test expansion if these new technologies can be integrated safely and effectively into newborn screening programs. One potential concern associated with expansion of screening panels is the impact on follow-up testing and tracking. If the proportion of false positive cases requiring additional tests that are identified in screening laboratories rises excessively, this could undermine the acceptance of such testing by both the parental and medical communities, as well as potentially diminish the cost benefit of additional testing.

Multiplex testing technologies are emerging that can simultaneously identify multiple analytes from a single analytical process. Some multiplex testing requires that an analytical target first be identified and placed in the multiplex test (e.g., genomic arrays). Other multiplex testing provides the additional testing information without the need for specific target selection (e.g., DNA sequencing). For example, testing for hemoglobinopathies by isoelectric focusing (IEF) provides information not only about hemoglobin S, the primary target of screening, but also about more than 700 other possible hemoglobin variants, some of which may be clinically significant (e.g., Hb C and E).[17]

In the case of MS/MS, the multiplex testing can occur in different modes, because it is possible to operate the instrument by either selecting specific targets or analyzing full profiles.[18] When used on selected targets, it is referred to as selective reaction monitoring (SRM), which is also called multiple reaction monitoring, a process that allows for the selective evaluation of specific ion species instead of a profile within a mass range. Increasingly, MS/MS is being used in newborn screening laboratories.[19] The technology is appealing for several reasons, including sensitivity for detecting ion species in low concentration, ability to quantify results relative to internal standards, high-throughput and precision, and the opportunity to simultaneously measure multiple ion species.[15,20] However, MS/MS is a complex testing platform requiring specific training and experience in order to optimize its use.[18]

Although multiplex testing allows the addition of many more conditions to a screening panel, it presents a series of issues that influence the screening and health care system, ultimately affecting the screening services that might be available to the public. The availability of multiplex testing increases the number of conditions that can be considered for newborn screening that otherwise might not have been considered for screening using traditional criteria, such as incidence and treatability. Thus, our perception of screening performance characteristics is also modified. For example, multiplex technology might also reveal clinically significant conditions other than those that were the primary targets of screening but which are determined in the course of diagnostic confirmation of the screening test results. The screening laboratory may not have optimized the screening for the detection of these other conditions but they are typically part of the differential diagnosis of a primary target condition. Rather than evaluate single conditions for their inclusion in newborn screening, we must now consider how best to use the additional information revealed in the diagnostic laboratory about other related conditions.

Although information about conditions for which treatment options are scarce or not yet reported can lead to increased stresses on families and the health care system, early information can also lead to knowledge of the condition for the family, thus avoiding a potential diagnostic odyssey or inappropriate therapies. In addition, early information provides opportunity for better understanding of disease history and characteristics, and for earlier medical interventions that might be systematically studied to determine the risks and benefits. Multiplex testing and the identification of conditions falling outside of the uniform screening panel provides the opportunity for such conditions to be included in research protocols. Therefore, the criteria used to include a condition in a mandated newborn screening panel are not necessarily straightforward scientific or clinical criteria, but often involve complex ethical, legal, and social policy decisions.

Aside from new multiplex technology for screening, there has also been the introduction of tiered testing strategies to enhance the positive predictive value of screening and reduce the number of infants referred for additional testing.[21] For example, in the United States, the primary analyte used for congenital hypothyroidism (CH) newborn screening has been thyroxin (T4), because most newborns are screened before the optimal time for screening with thyrotropin (thyroid stimulating hormone, TSH). TSH primary screening offers improved

specificity only after the period of neonatal surge and does not identify cases of central hypothyroidism. To decrease the recall rate, most screening programs have utilized a second-tier test with TSH following the identification of a certain number of increased-risk newborns through T4 initial testing.[22] In such cases, secondary hypothyroidism may also be detected on the basis of the test results, even though it is not the primary target of screening. Similarly, it has been shown that the rate of false positive results in CAH screening can be significantly reduced by profiling steroids by MS/MS as a second-tier test.[23]

In addition, the testing of specific DNA mutations in newborn screening (e.g., CF screening algorithms utilize a second-tier DNA mutation panel following initial screening for immunoreactive trypsinogen (IRT) and hemoglobinopathy screening algorithms that include DNA testing) can minimize the recall rates.[24] The testing of DNA mutations also has led to a new category that includes unaffected or minimally affected cases (e.g., carriers, benign hyperphenylalaninemias, and detection of hemoglobin Barts). Confirmation of such results and explanation of their significance can be costly. These examples highlight the ongoing process that occurs in newborn screening laboratories whereby analytes are identified that are clearly abnormal in a particular condition but still need to be analytically and clinically validated in a population screening setting.

#### The evidence based landscape

Assessing the evidence on conditions as to their appropriateness for newborn screening is complex, and there are limitations in the availability and interpretation of data about many of the conditions. The incidence of rare genetic diseases is often variable among different populations and can be biased by the nature of the populations involved in research and the severity of the conditions in those coming to the attention of health care professionals. Many of the conditions are ultra-rare and they may have multiple genetic etiologies. For instance, the tetrahydrobiopterin (BH4) deficiencies are a heterogeneous group of disorders that affect phenylalanine homeostasis.[25] BH4 deficiencies are detected as a by-product of screening for phenylketonuria due to hyperphenylalaninemia. They include disorders that affect the regeneration or biosynthesis of BH4. The condition referred to as biopterin cofactor biosynthesis defect is caused by one of two genes-GTP cyclohydrolase I (GTPCH) and 6-pyruvoyl-tetrahydrobiopterin synthase (PTPS)- and the condition referred to as biopterin cofactor regeneration defect is caused by one of two genes-pterin-4$\alpha$-carbinolamine dehydratase (PCD) and dihydropteridine reductase(DHPR). Due to the biochemical similarities of the deficiencies resulting from blocks in these interrelated pathways, the clinical courses are similar in those with the typical severe forms of GTPCH, PTPS, and DHPR deficiencies. Approximately 57% of the rare BH4 abnormalities involve PTPS deficiency. However, due to the similarities in phenotype and treatment, the BH4 abnormalities are commonly combined with the two aforementioned groups and the treatments are similar. Hence, incidence as it relates to the genetic etiology is usually combined for the two subtypes. Treatment for the conditions is related to the degree of hyperphenylalaninemia and to the degree of impairment of biogenic amine production, which varies among those affected. Further, a treatment involving BH4 administration is now approved in Europe, following clinical trials, that demonstrated that both GTPCH and PTPS are responsive to BH4. Due to the fact that GTPCH is very rare, yet quite similar to PTPS, the affected are aggregated when treatment is assessed. In any case, due to the rarity of these conditions, it is not until a very large general population has been identified through screening that penetrance and expressivity of disease are determined and a true incidence figure becomes available. In order to ensure that new therapies for these rare and severe genetic diseases will be available, regulatory agencies sometimes accept premarket evidence from smaller treatment groups while shifting the burden for the collection of additional information to FDA Phase IV postmarket surveillance, as was reported in FDA News for Fabrezyme® for the treatment of Fabry disease. (See http://www.fda.gov/bbs/topics/NEWS/2003/NEW00897.html)

Having such treatments available earlier means that it becomes increasingly difficult to collect information on the natural history of the untreated condition. In fact, there has not been a natural history study of PKU conducted since the 1970s because the affected infants are routinely identified in screening are treated, respond well to the treatment. Understanding the genetic basis of these conditions has led to this relatively rapid transition between ability to diagnose and the development of treatments based on the underlying biology and pathology of genetic diseases, particularly those that involve the replacement of defective enzymes. Hence, it becomes increasingly important to develop national systems for the collection of clinical information about those individuals identified in screening to further inform our understanding of the screened conditions and to further evaluate treatment modalities through an iterative process.

The assessment of the evidence on the performance characteristics (analytical and clinical sensitivity, specificity, and positive predictive values) of the tests, as used in newborn screening is complex. Many of the screening tests use technologies that are the gold standard in the diagnostic setting, such as HPLC or IEF for hemoglobinopathies or MS/MS for the acylcarnitine disorders. Although one can demonstrate very strong analytical and clinical performance in a diagnostic setting, clinical performance in screening is a function of the cut-offs that are used by the screening laboratories to capture the most affected persons. States often assign varying cut-offs to analyte levels and often use different screening test algorithms, including second-tier tests or repeat tests to arrive at a determination of whether the specimen is within the normal range, with highly variable case definitions at screening. This lack of standardization makes it quite complex to assign a level of performance to the screening tests at a national level or to compare the performance of programs.

Finally, the evidence base for newborn screening is complicated by the differing views of the interest groups involved. For purely scientific and medical issues, the scientific literature

provides objective information about different aspects of conditions, such as incidence, treatment efficacy, and diagnostic confirmation. However, some criteria have significant subjective aspects that require the consideration of more than just scientific and expert opinion. Cost is an example of a subjective criterion because it is a contextual concern and can only be measured against the value of the outcome. Other criteria may be perceived differently by the professional community or by other nonscientific or nonmedical interest groups. For example, parents often consider difficult the impact of treatments that health care professionals consider to be simple (e.g., maintaining a child on a specified diet). Some criteria are perceived differently among varying groups of professionals. For example, primary health care professionals in urban areas often have greater access to subspecialists than do those in rural areas. It is often difficult to balance the scientific evidence against the values that different groups place on newborn screening to reduce mortality and morbidity of diseases.

**The need for evaluation of newborn screening systems**

The lack of equitable newborn screening services offered for infants, the changing dynamics of emerging technology, and the complexity of genetics require an assessment of the state of the art in newborn screening and a perspective on the future directions such programs could take. In addition, programs must include an assessment of the availability of needed resources, both public and private, when determining which conditions should be included. A national, organized approach to differentiating among these many competing needs would help create a more informed process for deciding what tests should be included in newborn screening programs.

Since the first State newborn screening programs began, periodic assessments have been made. As early as 1968, the World Health Organization (WHO) issued a report urging that screening tests be appropriate and straightforward.[26] In 1975, the National Academy of Sciences (NAS) redefined genetic screening and established the fundamental principles and rules of procedure for genetic testing (these did not vary significantly from the 1968 WHO recommendations). NAS also made recommendations regarding the aims of testing and screening, criteria for testing, and the quality of testing.[13] In 1997, the Task Force on Genetic Testing, created by the National Institutes of Health-Department of Energy Working Group on Ethical, Legal and Social Implications of Human Genome Research, focused on the quality of testing and recommended that screening tests demonstrate analytical and clinical validity and utility[27] (Holtzman and Watson, 1997 available at http://www.genome.gov/10001733). In 1999, at the request of HRSA, AAP convened a Newborn Screening Task Force that provided a comprehensive evaluation of the current state of newborn screening programs in the United States.[13] The Task Force recommendations covered the public health and clinical care system, the roles of professionals and the public, issues of disease surveillance and research, and the economics of newborn screening. The report recommended that "HRSA should engage in a national process involving government, professionals, and consumers to advance the recommendations of this Task Force and assist in the development and implementation of nationally recognized newborn screening system standards and policies." In addition, the AAP Task Force[13] thought that greater uniformity would benefit families, health care professionals, and the newborn screening programs. In 2000, the March of Dimes, an organization that has advocated on behalf of newborn screening programs, recommended that tests be rapid, high quality, and accurate and that cost should not be a major consideration.[28] Subsequently, the March of Dimes recommended that all States screen for nine conditions plus newborn hearing loss (see www.marchofdimes.com/professionals/580.asp).

**B. Methods used for assessing conditions**

As an initial step in the process, ACMG convened a newborn screening expert group that included participants with expertise in various areas of subspecialty medicine, primary care, health policy, law, ethics and public health, and consumers. The expert group also formed two expert work groups to provide more in-depth analysis in two specific areas: the uniform panel and its criteria, and the diagnosis and follow-up system. Members of the expert group and work groups are listed at the beginning of this report. Work group members were selected based on their abilities to bring a strong scientific and clinical—rather than organizational—perspective to the issues under consideration. Not only were efforts made to ensure cultural, ethnic, and geographic diversity, there also were efforts to involve health care professionals and other interested parties from a wide range of fields and backgrounds, including expert representation from public health laboratories and program administration; individuals who are involved in the delivery of specialty care; primary care and nonphysician health care professional groups that are involved with the patients and families; and parents who have been directly affected by newborn screening programs.

The project depended on a variety of types of input obtained through expert reviews of the scientific literature, presentations from international and national invitees at six meetings of the expert group, solicitations for public and professional comment, and detailed assessments provided by the work groups. Considerable information was acquired through the use of disease-specific surveys that were broadly distributed and augmented by direct requests for input from acknowledged experts for the conditions under consideration. Areas in which deficiencies were found in the information available in the scientific literature were identified as well.

The expert group followed a two-tiered approach to assessing conditions that allowed for the views of experts of various types, including consumers, to be considered while still deferring to the evidence in the scientific literature. In the first level of the assessment, the expert group sought broad input through a survey of individuals and organizations with an interest in newborn screening. The expert group utilized a data collection instrument, distributed through a survey and directly to experts, to seek unpublished data and views related to

the criteria by which conditions were to be evaluated. The opinions of experts and others were quantified using the scoring system assigned to each criterion in the data collection instrument. Conditions were then placed preliminarily into categories reflecting their overall scores on the data collection forms. In the second level of the assessment, the scientific and medical evidence bases relating to the conditions under consideration were developed. Each condition was then reassessed to ensure that the evidence base confirmed that three critical evaluation categories were met in order to define a uniform panel of conditions to be targeted by newborn screening programs.

**Establishing principles for the development of newborn screening guidelines**

Many factors could influence a decision to include a given condition in a newborn screening program, including, for example, the severity of the condition, the availability of effective treatment, the age of onset, and the complexity or cost of the test.[29] In developing the criteria to evaluate conditions and make recommendations, the expert group relied on a set of basic principles developed at the onset of the project. The order of these principles is not intended to suggest a prioritization.

An overarching concept is utility—that is, an approach that delivers the greatest good to the greatest number of people, while recognizing the need for some flexibility and the use of alternative mechanisms by screening programs. Newborn screening policies and practices have national, regional, and local implications. Although national uniformity is a goal for newborn screening programs, there also may be a need, in limited and specific circumstances (such as meeting local and community public health needs), to screen for certain genetic conditions identified only in given populations.

Newborn screening involves many parties. In addition to the child and his or her family or guardian, these include public health officials, health care professionals, private insurers, government officials, researchers, policymakers, educators, and others. This report seeks to acknowledge the full range of participants involved.

1. **Universal newborn screening is an essential public health responsibility that is critical to improve the health outcome of affected children.**
   To ensure that all United States newborns have access to screening and to promote a systems approach to population-based health care, it is critical that newborn screening remain a public health function.
2. **Newborn screening policy development should be primarily driven by what is in the best interest of the affected newborn, with secondary consideration given to the interests of unaffected newborns, families, health professionals, and the public.**
   A key factor determining the inclusion of particular conditions in newborn screening programs is the potential for the affected newborn to realize a significant improvement in quality of life as a result of the screening. Although the expert group gives primary consideration to newborns that are being screened, it is clear that many others are also affected by newborn screening. Newborns that do not screen positive can benefit from the elimination of certain diagnoses, and families benefit independent of the newborn that was screened. Furthermore, because these programs can decrease mortality and morbidity, public health professionals, the public, and the health care system may derive benefits from newborn screening programs, such as cost reductions for overall health care services. There may also be negative consequences for newborns and families that result from screening, including the potential negative impact of a false-positive screening result. Aside from the financial cost of a medical work-up to confirm that a suspected condition does not exist, there may be associated anxiety and stress for the family.
3. **Newborn screening is more than testing. It is a coordinated and comprehensive system consisting of education, screening, follow-up, diagnosis, treatment and management, and program evaluation.**
   To realize the benefits from newborn screening, all components of the program must function well together. The six critical components of newborn screening programs—education, screening, follow-up, diagnosis, treatment and management, and evaluation—are important to the overall functioning of individual newborn screening programs and the system in which they operate.[30] There must be assurance of timely and accurate reporting and tracking of abnormal results. In order to know whether a program is functioning effectively and efficiently, it is important to know whether the expected health benefits are being realized.
4. **The medical home and the public and private components of screening programs should be in close communication to ensure confirmation of test results and the appropriate follow-up and care of identified newborns.**
   The medical home concept has evolved as the central focus for the care of patients in their communities and should be the center of communication, primary care, and coordination of care for individuals.[31] There is increased recognition that enhanced communication between the clinical care system and public health programs is necessary to ensure optimal care and outcomes for the affected newborns. It is essential to establish close communication among State public health programs, the newborn's medical home, and the subspecialists commonly involved in the diagnosis and follow-up of affected newborns.
5. **Recommendations about the appropriateness of conditions for newborn screening should be based on the evaluation of scientific evidence and expert opinion.**
   There are ever-increasing numbers of relatively rare conditions for which clinical knowledge is rapidly growing but for which the published literature may be

sparse or outdated. Moreover, clinical expertise in treating many of these conditions may be limited. Given that all screening programs must rely on the same published knowledge base and a limited number of experts, a national process of scientific evaluation seems most practical. As new evidence emerges and opinions change, there should be a system in place for prompt review and release of updated recommendations.

In 2003, the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was established by the Department of Health and Human Services (DHHS). Its mandate was to advise and guide the Secretary of DHHS regarding the most appropriate application of universal newborn screening tests, technologies, policies, guidelines, and programs in order to effectively reduce morbidity and mortality in newborns and children who have or who are at risk for heritable disorders. The committee's purpose is to provide the Secretary with: ".advice and recommendations concerning the grants and projects and technical information needed to develop policies and priorities that will enhance the ability of State and local health agencies to provide for newborn and child screening and counseling and health care services for newborns and children having or at risk for heritable disorders." (Available at http://mchb.hrsa.gov/programs/genetics/committee/)

6. **To be included as a primary target condition in a newborn screening program, a condition should meet the following minimum criteria:**
   - It can be identified at a period of time (24 to 48 hours after birth) at which it would not ordinarily be clinically detected.
   - A test with appropriate sensitivity and specificity is available.
   - There are demonstrated benefits of early detection, timely intervention, and efficacious treatment.

   Determining the appropriateness of a condition for newborn screening is a complex process. Although the emergence of new technologies such as MS/MS has altered views of which conditions should be included in mandated screening programs, in this report the primary targets of screening are those that meet the three criteria previously specified. A secondary target is one that is identified while searching for the primary target (e.g., HbC results from IEF while looking for HbS) or a clinically significant condition that is likely to be detected when performing a comprehensive profile of a given group of biochemical markers (e.g., GA2 may be identified while determining MCAD status (C8 acylcarnitine is elevated in both)).
7. **The primary targets of newborn screening should be conditions that meet the criteria listed in #6 above. The newborn screening program should report any other results of clinical significance.**

   Many technologies can be applied to screening for primary targeted conditions. Some allow for more than one condition to be identified in a single procedure, and some provide important information about the presence of conditions that may not meet all of the criteria needed to be considered a primary target condition. The advent of molecular arrays and MS/MS has significantly broadened this potential. It is not necessarily the responsibility of the screening program to monitor the long-term follow-up of patients identified with clinically significant conditions that are not the primary targets of newborn screening. However, the significant costs of the diagnostic odysseys that may ensue following the birth of a child whose condition may have been suspected based on newborn screening results, and the related costs to families and the system of introducing futile therapies might be avoided if clinically significant results from newborn screening programs are shared with the newborn's primary caretaker.
8. **Centralized health information data collection is needed for longitudinal assessment of disease-specific screening programs.**

   Mechanisms and systems that allow for the collection of short- and long-term data on affected individuals while protecting their right to privacy will allow for assessment and improvement of program performance and individual health outcomes. The pooling of information about health outcomes, treatment protocols, case definitions, and diagnosis and confirmation algorithms will improve care for the infants identified in the programs. Furthermore, it is often difficult to ascertain the natural history of rare diseases because of their low frequency and because they often exhibit genetic variability in severity and expression. Hence, data collection and shared data evaluation can significantly inform program decision-making and medical science. General population data are also needed to better understand certain approaches to screening (e.g., genomics), where the variability in expression of mutations is not entirely clear until individuals without the classical presentation of a condition are tested.
9. **Total quality management should be applied to newborn screening programs.**

   As with any programmatic effort, improvements result from careful and continuous monitoring of key steps in the process, the assessment of that information, and the introduction of changes that continuously improve program performance. Uniform and consistent monitoring of system quality indicators can provide information about the relative performance of screening programs.
10. **Newborn screening specimens are valuable health resources. Every program should have policies in place to ensure confidential storage and appropriate use of specimens.**

    Specimens obtained for newborn screening have tre-

mendous long-term value. They can be used for purposes of program quality management, to help inform deliberations about program expansion, for research on testing technology and treatment, and for epidemiologic studies. This is not to imply that every State should store all specimens forever but, rather, that there should be a sufficient number of States with diverse populations and long-term storage of residual specimens to provide this critical resource. Regardless, it is important to ensure the confidentiality of those persons whose specimens are stored. The use of specimens for nontherapeutic purposes must not alter the willingness of the public to participate in newborn screening programs and related activities.

11. **Public awareness, coupled with professional training and family education are significant program responsibilities that must be part of the complete newborn screening system.**
Because newborn screening can have a significant impact on health outcomes for affected newborns, it is essential that the public as well as health care and public health professionals be informed of the availability of the programs and of changes that are made. Education and awareness are essential to both the quality of the screening programs and participation by the public and by health care professionals. As such, information sharing and education are critical program responsibilities.

### Choosing the conditions

Eighty-four conditions were evaluated using these criteria (see Table 1). The conditions were chosen for several reasons. Any condition currently included in private, State, or national newborn screening programs was considered. Other conditions were included because they are known to be coincidentally revealed by some of the technologies used in newborn screening. Still others were identified by members of the public, the expert group, and work groups as worthy of consideration because they are important from a public health standpoint and/or there is a high level of public and/or scientific interest in screening for the condition. Hemoglobinopathy screening was mainly driven by the conditions associated with a hemoglobin S allele. Among these, Hb SS, Hb SC and Hb S$\beta$-thalassemia were considered separately. Variant hemoglobinopathies included other conditions associated with an Hb S allele. Additional hemoglobinopathies revealed by screening, such as Hb E, are not the conditions to which screening currently is targeted. As discussed below, compromises were made in the lumping or splitting apart of conditions to be listed for assessment.

To a limited extent, the conditions listed as considered by the expert group represent a compromise among the various options. The intent was to distinguish many of the more common forms of the condition from others though there are still situations in which some very rare conditions are subsumed under a more general name for the condition.

The group considered it important to fully assess all conditions and to ensure that any apparent deficiencies were properly recognized so that disease-specific advocacy groups and the research community could focus on these deficiencies in developing their research agendas.

### Developing evaluation criteria and their comparative values

Generally, a medical condition is assessed by itself to determine whether it should be included in a public health newborn screening program,[14,29] rather than being assessed along with a number of other conditions in a way that would allow for comparative ranking. Historically, this is primarily because individual conditions have been identified by individual testing platforms. Although conditions have usually been compared on the basis of relative incidence, there was little need for additional discriminating criteria given the general availability of traditional testing methodologies and treatments. Thus, comparative analyses of screened conditions or evaluations of the scientific evidence for or against inclusion of the conditions have not been formally conducted nationally, though this has often been done within individual programs.

Until recently, the capability of the currently available testing technology limited the conditions that could reasonably be included in a screening panel. Now, however, new information emerging from the clinical and scientific literature, combined with evolving technologies, has made it possible for increasing numbers of rare conditions to be detected simultaneously from single screening tests, making it reasonable to attempt more complex relative comparisons when deciding on conditions that should be added to a screening panel. Thus, it is no longer a simple matter to decide which condition should be added to a screening panel based on incidence, when a group of conditions may be simultaneously detected from a single analytical procedure and the group incidence (or impact to society) may be of higher relative importance than any of the single conditions within the group. In addition, even if multiple conditions could be detected, the question of whether they *should* be detected remains, when, for example, no efficacious treatment exists. Increasing the complexity of this decision-making process is the fact that all of the conditions detected may not have similar clinical outcomes for all children.

In recent years, professional groups in other countries have attempted to develop an organized, national approach to determining which conditions should be included in newborn screening panels. The Health Technology Assessment Program of the National Health Service of the United Kingdom has initiated a national program to systematically review the scientific and medical literature on inborn errors of metabolism, neonatal screening technology, and screening programs. Their goal is to analyze the costs and benefits of introducing MS/MS-based screening of amino acid disorders, fatty acid oxidation defects, and organic acid disorders, as well as other conditions screened on an individual test basis within the United Kingdom health system.[10] This extensive analysis assigned weights to various aspects of specific conditions and their associated

**Table 1**
Individual conditions considered in the data collection instrument

| Group | | Condition | Code |
|---|---|---|---|
| | Endocrinology | Congenital adrenal hyperplasia | CAH |
| | | Congenital hypothyroidism | CH |
| | | Diabetes mellitus, insulin dependent | IDDM |
| | Hematology, Hemoglobinopathies | Hb SS disease (Sickle cell anemia) | Hb SS |
| | | Hb S/C disease | Hb S/C |
| | | Hb S/$\beta$ -thalassemia | Hb S/ß-Thal |
| | | Other variant Hb-pathies (including Hb E) | Var Hb |
| | | Glucose-6-phosphate dehydrogenase deficiency | G6PD |
| | Infectious Diseases | Human HIV infection | HIV |
| | | Congenital toxoplasmosis | TOXO |
| | | Congenital cytomegalovirus infection | CMV |
| | | Alpha 1-antitrypsin deficiency | A1AT |
| | | Adenosine deaminase deficiency | ADA |
| | | Biliary atresia | BIL |
| | | Cystic fibrosis | CF |
| | | Duchenne and Becker muscular dystrophy | DMD |
| | | Familial hypercholesterolemia (heterozygote) | FHC |
| | Miscellaneous Genetic Conditions | Fragile X | FX |
| | | Hearing loss | HEAR |
| | | Hyperbilirubinemia* | HPRBIL |
| | | Neuroblastoma | NB |
| | | Severe combined immunodeficiency | SCID |
| | | Turner syndrome | TURNER |
| | | Wilson disease | WD |
| Inborn Errors of Metabolism | Amino Acid Disorders | Phenylketonuria | PKU |
| | | Benign hyperphenylalaninemia | H-PHE |
| | | Defects of biopterin cofactor biosynthesis | BIOPT BS |
| | | Defects of biopterin cofactor regeneration | BIOPT REG |
| | | Homocystinuria | HCY |
| | | Hypermethioninemia | MET |
| | | Maple syrup (urine) disease | MSUD |
| | | Tyrosinemia type I | TYR I |
| | | Tyrosinemia type II | TYR II |
| | | Tyrosinemia type III | TYR III |
| | | Carbamylphosphate synthetase deficiency | CPS |
| | | Ornithine transcarbamylase deficiency | OTC |
| | | Citrullinemia | CIT |
| | | Citrullinemia type II | CIT II |

(continued)

**Table 1**
Continued

| Group | | Condition | Code |
|---|---|---|---|
| Inborn Errors of Metabolism | | Argininosuccinic acidemia | ASA |
| | | Argininemia | ARG |
| | Carbohydrate Disorders | Classic galactosemia | GALT |
| | | Galactokinase deficiency | GALK |
| | | Galactose epimerase deficiency | GALE |
| | | Congenital disorder of glycosylation type Ib | CDG Ib |
| | Fatty Acid Oxidation Disorders | Carnitine uptake defect | CUD |
| | | Carnitine palmitoyltransferase Ia deficiency (L) | CPT IA |
| | | Carnitine palmitoyltransferase Ib deficiency (M) | CPT IB |
| | | Carnitine/acylcarnitine translocase deficiency | CACT |
| | | Carnitine palmitoyltransferase II deficiency | CPTII |
| | | Very long-chain acyl-CoA dehydrogenase def. | VLCAD |
| | | Long-chain 3-OH acyl-CoA dehydrogenase def. | LCHAD |
| | | Trifunctional protein deficiency | TFP |
| | | Dienoyl-CoA reductase deficiency | DE-RED |
| | | Glutaric acidemia type II | GA2 |
| | | Medium-chain acyl-CoA dehydrogenase deficiency | MCAD |
| | | Medium/short-chain 3-OH acyl-CoA DH def. | M/SCHAD |
| | | Medium chain ketoacyl-CoA thiolase deficiency | MCKAT |
| | | Short-chain acyl-CoA dehydrogenase deficiency | SCAD |
| | Lysosomal Storage Diseases | Fabry disease | FABRY |
| | Krabbe disease | KRABBE | |
| | Pompe disease | POMPE | |
| | Hurler-Scheie disease | MPS-1H | |
| | | Lysosomal storage diseases | LSD |
| | Organic Acid Disorders | Propionic acidemia | PA |
| | | Multiple carboxylase deficiency (Holocarboxylase Synthetase deficiency) | MCD |
| | | Methylmalonic acidemia (mutase) | MUT |
| | | Methylmalonic acidemia (Cbl A, B) | Cbl A,B |
| | | Methylmalonic acidemia (Cbl C,D) | Cbl C,D |
| | | Isobutyryl-CoA dehydrogenase deficiency | IBG |
| | | 2-Methylbutyryl-CoA dehydrogenase deficiency | 2MBG |
| | | 2-Methyl 3-hydroxy butyric aciduria | 2M3HBA |
| | | $\beta$-Ketothiolase deficiency | $\beta$KT |
| | | Isovaleric acidemia | IVA |
| | | 3-Methylcrotonyl-CoA carboxylase deficiency | 3MCC |
| | | 3-Methylglutaconic aciduria | 3MGA |
| | | 3-hydroxy 3-methyl glutaric aciduria | HMG |
| | | Glutaric acidemia type I | GA I |
| | | Malonic aciduria | MAL |

(continued)

**Table 1**
Continued

| Group | Condition | Code |
|---|---|---|
| Other IEM | Biotinidase deficiency | BIOT |
| | X-linked Adrenoleukodystrophy | ALD |
| | Smith-Lemli-Opitz syndrome | SLO |
| | Guanidinoacetate methyltransferase deficiency | GAMT |
| | Arginine: glycine amidinotransferase deficiency | AGAT |
| | Creatine transporter defect | CR TRANS |

NOTE: Neonatal hyperbilirubinemia (Kernicterus) (code HPRBIL) was added to this list after the completion of the data collection instrument.

tests and treatments, and assigned a qualitative value to the published information available. This effort has highlighted the difficulties inherent in attempts to balance costs and benefits against the value that the public and families place on such screening.

The Human Genetics Society of Australasia developed criteria for placing conditions into one of four tiers. These tiers are determined by the nature of the benefit of the screening to the newborn, the benefit of the screening balanced against the cost, the suitability of the test, and the availability of appropriate and organized diagnostic and follow-up services (available at http://www.hgsa.com.au/Word/HGSApolicyStatementNewborn-Screening0204-18.03.04.doc).

More recently, Belgium has sought to assign values to the Wilson and Jungner criteria,[14] in order to weigh conditions against each other (see Box 1). Although novel, this system was considered to be less detailed than needed because many of the Wilson and Jungner criteria are subjective and therefore less amenable to the application of a metric and therefore quantification.

In the United States, several states, including Nebraska, Tennessee, and Washington, recently developed criteria and systems for assessing and comparing conditions. With the establishment of the 2003 federal Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children, the potential for development of national policies and recommendations should lead to a more uniform or equitable approach to newborn screening.

None of the existing systems allowed for adequate comparative analysis of conditions being considered for newborn screening. Further, the evolution of screening programs and the screening technologies used have added new variables to be considered when assessing conditions. The ACMG expert group chose to develop a modified system for the assessment of conditions for their appropriateness for newborn screening.

The Uniform Panel Work Group developed the data collection instrument to use during the project's first phase to quantitatively evaluate the features of conditions under consideration for inclusion in a potential uniform screening panel. Using a weighted scoring system, the conditions were evaluated according to criteria in three main categories:

1. The clinical characteristics of the condition;
2. The analytical characteristics of the test; and
3. Diagnosis, follow-up, treatment, and management of the condition.

Within each of these categories, 19 component criteria including six characteristics of the analytical tests were considered for assigning a comparative value, or score. Conditions already included in newborn screening programs were used to model the scoring system. Each of the criteria was weighted to reflect the presumed importance of the particular criteria to the overall assessments of conditions. Experts in the conditions under consideration for newborn screening were then asked to consider the criteria and the extent to which they cover the range of issues that arise among disparate types of conditions. They were also asked to

**Box 1 Wilson and Jungner Criteria for Appraising the Validity of a Screening Program**

1. The condition being screened for should be an important health problem.
2. The natural history of the condition should be well understood.
3. There should be a detectable early stage.
4. Treatment at an early stage should be of more benefit than at a later stage.
5. A suitable test should be devised for the early stage.
6. The test should be acceptable.
7. Intervals for repeating the test should be determined.
8. Adequate health service provision should be made for the extra clinical workload resulting from screening.
9. The risks, both physical and psychological, should be less than the benefits.
10. The costs should be balanced against the benefits. SOURCE Wilson, J.M., and G. Jungner. *Principles and Practice of Screening for Disease.* (Public Health Paper Number 34.) Geneva: World Health Organization, 1968.

consider whether appropriate weights were assigned to criteria, thereby acknowledging the criteria considered most relevant. The language describing the criteria and the scores associated with the range of responses to the criteria were adjusted by the expert group (see Table 2 for the criteria and the possible scores). Then, the weight accorded to each criterion was revised (i.e., the highest possible score within each category was the same). The criteria that were identified within each category were assigned a range of possible responses and related scores ranging from 0 to a maximum score that varied according to each criterion's overall importance. Conditions already included in newborn screening programs were then assessed for their performance in the system. Results were compared with those obtained by other systems developed for this purpose to determine whether the outcomes were similar.

The scoring system recognizes the strengths and limitations found in each condition and summarizes them in a ranking system. Thus, a low score in a particular area does not necessarily mean that screening for that condition will never be conducted. In fact, low scores could be radically overruled by scientific evidence of new advances in testing and treatment and should be recognized as opportunities for targeted clinical or basic research endeavors and subsequent reconsideration of the condition for inclusion.

The criteria that were developed to differentiate the appropriateness of conditions for newborn screening include some

**Table 2**
Combined criteria and distribution of scores in the data collection instrument(Highest possible score: 2100)
I. Condition/Disorder (subtotal score 700)

| Criterion | Categories in criterion | Score |
|---|---|---|
| Incidence of condition | >1:5x000 | 100 |
| | >1:25,000 | 75 |
| | >1:50,000 | 50 |
| | >1:75,000 | 25 |
| | <1:100,000 | 0 |
| Signs and symptoms clinically identifiable in the first 48 hours | Never | 100 |
| | <25% of cases | 75 |
| | <50% of cases | 50 |
| | <75% of cases | 25 |
| | Always | 0 |
| Burden of disease (natural history if untreated) | Profound | 100 |
| | Severe | 75 |
| | Moderate | 50 |
| | Mild | 25 |
| | Minimal | 0 |
| Individual benefits of early intervention | Clear scientific evidence that early intervention resulting from screening optimizes outcome | 200 |
| | Some scientific evidence that early intervention resulting from screening optimizes outcome | 100 |
| | No scientific evidence that early intervention resulting from screening optimizes outcome | 0 |
| Familial and societal benefits of early intervention | Early identification provides clear benefits to family and society (education, understanding prevalence and natural history, cost effectiveness) | 100 |
| | Early identification provides some benefits to family and society | 50 |
| | No evidence of benefits | 0 |
| Early diagnosis and treatment prevent mortality | Yes | 100 |
| | No | 0 |

**Table 2**
Continued
II. Screening Test (subtotal score 700)

| Criterion | Categories in criterion | Score |
|---|---|---|
| Does a sensitive AND specific screening test algorithm currently exist? | Yes | 200 |
| | No | 0 |
| Test characteristics (Yes = apply score; No = 0) | Doable in neonatal bloodspots **OR** by a simple, in-nursery physical method | 100 |
| | High throughput (>200/day/FTE) | 50 |
| | Overall analytical cost <1$ per test per condition | 50 |
| | Multiple analytes relevant to one condition are detected in same run | 50 |
| | Other conditions identified by same analytes | 50 |
| | Multiple conditions detected by same test (multiplex platform) | 200 |

III. Treatment & Management (subtotal score 700)

| Criterion | Categories in criterion | Score |
|---|---|---|
| Availability of treatment (*) | Treatment exists and is widely available in most communities | 50 |
| | Treatment exists but availability is limited | 25 |
| | No treatment available or necessary | 0 |
| Cost of treatment (*) | Inexpensive | 50 |
| | Expensive (>$50,000/patient/year) | 0 |
| Potential efficacy of existing treatment | To prevent ALL negative consequences | 200 |
| | To prevent MOST negative consequences | 100 |
| | To prevent SOME negative consequences | 50 |
| | Treatment efficacy not proven | 0 |
| Diagnostic confirmation | Providers of diagnostic confirmation are widely available | 100 |
| | Limited availability of providers of diagnostic confirmation | 50 |
| | Diagnostic confirmation is available only in a few centers | 0 |
| Acute management | Providers of acute management are widely available | 100 |
| | Limited availability of providers of acute management | 50 |
| | Acute management is available only in a few centers | 0 |
| Simplicity of therapy | Management at the primary care or family level | 200 |
| | Requires periodic involvement of a specialist | 100 |
| | Requires regular involvement of a specialist | 0 |

NOTE: The two criteria marked with (*) above were combined in the data collection instrument, a score of 100 was attributed to a treatment that is inexpensive and widely available, 50 if expensive or limited availability, 0 if expensive and limited availability. The final version was prompted by feedback from several survey respondents who felt that not all options were actually considered (e.g., no treatment necessary).

that have a highly objective scientific basis and others that are more subjective. To the extent possible, the expert group relied on the scientific literature to provide the information on which its recommendations are based. Survey respondents were provided with the data collection instrument, questionnaires about the criteria themselves, the weight assigned to criteria, and the distribution of scores within a criterion. The respondents were asked to provide information on both objective and subjective criteria as a way of determining a respondent's familiarity with the condition(s).

## THE THREE MAIN CATEGORIES AND THEIR CRITERIA

### Clinical characteristics of the condition

Three criteria were developed for this category:

1. **Incidence Of The Condition**
   The incidence of the various conditions varies widely. In terms of public health importance, the more common the condition, the higher the justification for screening. Accordingly, any condition with a documented (or estimated) incidence of 1:100,000 or less received a score of zero, while an incidence of 1:5,000 or more received a score of 100. When technology allows for the condition to be detected in the course of screening for other conditions, points were added back through the appropriate testing criteria. (See "Screening Test: Availability and Characteristics," below.)
2. **Clinically Identifiable Signs And Symptoms In The First 48 Hours**
   In the context of public health, it is more important to screen for conditions that generally would not be detected in the newborn period based solely on routine clinical evaluation. However, it is important to recognize that there could be differences of opinion regarding whether a particular phenotype could be recognized by a typical health care provider and/or specialist, and the phenotypic variability expected among newborns with a particular condition must be considered. Nonetheless, if clinical symptoms are never detectable within 48 hours after birth, the condition received a score of 100. If clinical manifestations are always detectable, the condition received a score of zero.
3. **Burden Of Disease (Natural History If Not Treated)**
   This is an important criterion for prioritizing the use of public health resources because it favors screening for conditions that constitute greater burdens to those affected (if the burden is profound, for example, a score of 100 was given). It is recognized that some conditions have a wide range of severity and that the test may not necessarily discriminate the milder forms from the more severe forms.

#### The screening test: availability and characteristics

Seven criteria are included in this category:

1. **Availability Of A Sensitive And Specific Test Algorithm**
   This criterion is a central consideration when assigning a test or a condition to a uniform screening panel. The expert group chose to define this criterion as a test algorithm because some tests might require that additional analytes or second-tier tests be incorporated to achieve sufficient specificity (e.g., the use of T4 and TSH for the screening of CH or the use of a second-tier molecular test to improve the specificity of the IRT test for CF). This criterion was considered the first step in a decision tree without which further consideration for inclusion in newborn screening would not be possible. One hundred points were allotted to this feature of a condition. If a condition had no sensitive and specific test available that could be used in population screening, it was assigned a score of zero. However, it is acknowledged that there is no agreed-upon level of sensitivity and specificity and that this may vary with the burden of the condition and its importance for screening.
2. **Ability To Test On Either Neonatal Bloodspots Or An Alternative Specimen Type Or By A Simple, In-Nursery Procedure**
   Value was assigned if a test can be done on a dried bloodspot, which is a highly stable specimen type already integrated into newborn screening and on which many tests can be performed. Equal consideration was given to a screening test that could be conducted using a simple procedure or method, as with hearing screening, that would be appropriate for population screening. One hundred points were allotted to this feature of a test.
3. **Test Is Based On A Platform That Offers High-Throughput Capability**
   Value was placed on the ability of a technology to operate in a high-throughput format that allows testing of at least 200 specimens per full-time employee equivalent per day. The ability to test a large number of specimens in a short time offers cost savings to programs and increases efficiency, both important for public health screening. Fifty points were allotted to this criterion.
4. **Cost Of Test Is Less Than $1 Per Infant Screened**
   Value was placed on low-cost technologies. Cost was based on the personnel, reagents and other costs associated with testing only. Differences in the scoring of conditions detected by MS/MS were likely due to higher costs when a multiplex technology is used to screen for only a few conditions rather than for a larger number of conditions. Fifty points were allotted to this feature of a test.
5. **Multiple Analytes Relevant To One Condition Can Be Detected In The Same Run**
   The ability to detect multiple markers of a given condition within the same test increases the specificity of the method by allowing the calculation of ratios that have been shown to improve the differentiation between true positives and potential false positives. Fifty points were allotted to this feature of a test.
6. **Other Conditions (Secondary Targets) Can Be Identified By The Same Analytes**
   Value was assigned to the ability of a test to provide information about multiple conditions using the same analyte(s). Although these secondary targets may not independently meet all of the other criteria for inclusion in the uniform screening panel, they add value to the primary target condition because their detection constitutes a clinically significant result leading to tangible benefits to the affected newborn, family, and society. Fifty points were allotted to this feature of a test.
7. **Multiple Conditions Can Be Detected By The Same Test (Multiplex Platform)**
   Technology can add value to testing, particularly if it provides the ability to screen for many conditions in a single test. This can have public health importance above and beyond the features of the disease itself (i.e., by detecting

secondary conditions). This capability resides in technologies such as MS/MS, IEF, and HPLC for hemoglobin variants, DNA arrays used in sequencing, and labeled bead technologies. Technologies with multiplexing capability offer improved efficiency and cost-effectiveness to programs. Because of the public health importance of technologies with multiplex capabilities, this criterion was allotted two hundred points.

#### Diagnosis, follow-up, treatment, and management

Nine criteria were developed to assess the combined aspects of diagnostic confirmation and treatment and management:

1. **Availability Of Treatment**
   The availability of treatment is considered an important criterion for conditions in a core newborn screening panel. Fifty points were allotted to this feature of a condition, though additional value is assigned later depending on the effectiveness of the treatment.
2. **Cost Of Treatment**
   The cost of treatment is an important consideration in newborn screening. Although this criterion does not necessarily differentiate cost from value, it should be factored into decision-making. Fifty points were allotted to this feature of the treatment.
3. **Potential Efficacy Of Existing Treatment**
   More effective preventive or therapeutic interventions for a given condition increase the value of testing. For many conditions, treatments could result in near normal or normal outcomes. For others, the treatment may affect only a subset of the negative phenotypes possible or allow for only incremental improvements in optimal outcome. Moreover, treatment might not be equally effective in all individuals. This was considered a critical criterion and was assigned a value of 200 points.
4. **Individual Benefits Of Early Intervention**
   This criterion is important because the benefit to the child being screened is the overriding consideration. This was considered an objective criterion based on the quality of available evidence showing that early intervention optimizes outcome. Two hundred points were allotted to this feature of a treatment.
5. **Familial And Societal Benefits Of Early Identification**
   Early identification of an infant with a condition can bring benefits to families and/or society beyond the prospect of treatment. Because so many of the conditions detected through newborn screening are genetic, families can benefit from establishing that there may be a genetic risk to others in the family. Society could benefit by a reduction in medical diagnostic odysseys that are costly to the health care system. One hundred points were allotted to this feature of a condition.
6. **Prevention Of Mortality Through Early Diagnosis And Treatment**
   Prevention of mortality was assigned a value independent of reduction of morbidity. One hundred points were allotted to this feature of a condition.
7. **Availability Of Diagnostic Confirmation**
   Many conditions included in newborn screening programs are rare, and there may be poor access to diagnostic confirmation testing in the United States or even internationally. In such cases, it is more difficult to follow-up on cases with positive results, and the results provided by research laboratories may be more difficult to interpret and communicate to child health professionals and families than those from diagnostic laboratories. Furthermore, in the United States it may be ethically or legally problematic to report results from tests conducted by laboratories that are not certified by the Clinical Laboratory Improvement Amendments (CLIA). On the other hand, some conditions can be confirmed locally because of the wide availability and relative simplicity of the confirmatory test or service. Thus, different values were assigned based on the ease of diagnostic confirmation. One hundred points were allotted to this feature of a condition.
8. **Acute Management**
   As with diagnostic confirmation, the availability of health care professionals who have expertise in the acute management of the condition could be limited. Thus, higher values were assigned to conditions for which acute disease management is readily available. One hundred points were allotted to this feature of a condition.
9. **Simplicity Of Therapy**
   Therapeutic interventions range from highly specialized (e.g., bone marrow/umbilical cord blood transplantation) to extremely simple (e.g., vitamin supplementation, avoidance of fasting). A higher value was assigned to simpler therapies since simplicity determines whether infants requiring follow-up can be managed locally or whether subspecialist care is required. The acute management of many metabolic disorders often requires the involvement of metabolic disease physicians who are not readily available in many geographic locations. On the other hand, for example, aspects of CH may be managed by child health professionals, and when specialists are required, they are more widely available. Some conditions also might allow for greater levels of family involvement in treatment. One hundred points were allotted to this feature of a condition.

### Collecting the data

One goal of the data collection process was to include a broadly representative group of participants. A second goal was to use a method that would allow quantification of expert opinion. In addition to data gleaned from the scientific literature, input and opinion were sought from a wide array of child health professionals, subspecialty care experts and individuals interested in newborn screening. Respondents were not anonymous, and were asked to select one or more of the following

categories to describe their personal and/or professional role(s) in relation to newborn screening:

1. Provider of screening services (TESTING)
2. Provider of screening services (FOLLOW-UP)
3. Provider of screening services (ADMINISTRATION)
4. Provider of screening services (POLICY)
5. Provider of diagnostic services
6. Child health professional
7. Specialty care provider
8. Consumer

As discussed previously, many criteria were perceived differently by these diverse constituencies. Distinguishing among respondents allowed the expert group to independently assess the views of these different groups.

For each condition, steps were taken to ensure that those asked to provide information and those who provided information were broadly representative of the interest groups involved. A large number of acknowledged experts for each condition and specific consumer and professional organizations were asked to provide input through multiple professional groups (e.g., the Society for Inherited Metabolic Disease (SIMD), ACMG). Individuals from public health and newborn screening programs were offered the opportunity to participate through listservs of their representative organizations. This included listservs managed by HRSA/MCHB, NNSGRC, the Association of Public Health Laboratories, and others. To ensure that the perspectives of consumers were available for consideration, consumers were reached through listservs of NNSGRC, Genetic Alliance, and others. To ensure that there were several scientific and clinical experts for each condition, specific individuals were identified from recent publications, disease support groups, and professional groups. In addition, the data collection instrument used was made widely available through the ACMG web site (www.acmg.net). Due to the large and overlapping numbers of individuals participating in these listservs, it is not possible to state the number of potential participants who were contacted. Geographic origin and role or interest in newborn screening of survey participants was monitored to ensure that respondents were broadly representative.

Respondents were given the opportunity to score each criterion or mark it as unknown "U," an important option, because not all of those asked to participate were sufficiently familiar with the many aspects of all of the diseases for which responses were sought. However, the option also had implications for how the data were aggregated for analysis. The data were analyzed as means and medians for each criterion, as the average of total scores for each responder, and as sums of means and medians of all respondents to a particular criterion. After considering these different possibilities, it was decided that the results for any given condition would be expressed as the sum of the mean of the scores for each criterion. (The difficulty with using the sums of the means arises from different numbers of scorers, and scores varying in the comparisons, which obscures the distribution and confidence intervals of the final scores. The alternative approach using the sum of the medians was not used as the primary statistic because it tends to minimize dissent from the consensus. In later figures, conditions are ordered around the sum of the means and medians are otherwise shown. However, as previously discussed, for purely objective criteria, the data as evidenced by the scientific literature was applied and included in the sums rather than the survey information.)

#### Developing and integrating the evidence base

In the second tier of the assessment, the evidence base for the conditions was established and an algorithm through which conditions were reassessed was developed. The quantification of expert opinion or scoring system then becomes part of a broader assessment of the scientific literature related to the conditions, tests, and treatments in the second level of the assessments. The evidence from the scientific literature, with supporting references for each criterion of each condition, was reviewed as shown in the fact sheets (Appendix 1). Evidence was derived from a systematic review of:

1 Clinical evidence;
2. Cost/economic evidence and modeling;
3. Reference lists obtained from PubMed and Medline;
4. Books;
5. Health technology assessments commissioned by the U.K. National Screening Committee;
6. The Internet, including disease-specific support groups; and
7. Professional guidelines.

Epidemiology studies, when available, were assessed for study design, the nature of the subjects and the outcomes that were measured, and the effectiveness of the treatment.

Statistical analysis of survey results allowed for a score to be assigned to each condition which determined its ranking and initial placement in one of three categories (high scoring, moderately scoring, and low scoring or lacking a newborn screening test). After the assignment of conditions to one of the three categories, the evidence base on the condition, as validated by acknowledged experts in the conditions in question, was used to determine if the conditions met critical criteria categories. Experts in specific conditions were identified by the Conditions and Criteria Work Group and included many individuals who had participated in the data collection process.

Several critical criteria were identified that reflected the priorities and principles of the expert group. These include:

1. The existence of a sensitive and specific test that has been validated in a large general population;
2. The availability of an efficacious treatment;
3. A determination that the natural history was sufficiently well understood to justify placement in a core panel of conditions;
4. Determination of whether a clinically significant condition not in the core panel would be identified because it is part of the differential diagnosis of a core panel condition; and

5. Whether a clinically significant condition would be revealed by a multiplex technology and whether it was part of the differential diagnosis of a core panel condition.
6. Further, it was recognized that some tests allow for the definitive identification of unaffected carriers, and that such results should be communicated to a responsible individual in the health care system.

The fact sheets for each condition were reviewed by at least two experts for each condition to validate the information and assign a level of quality to the evidence. Levels of evidence correspond to those defined by the AAP Steering Committee on Quality Improvement and Management[32] as follows:

Level 1: Evidence is derived from well-designed randomized controlled trials or diagnostic studies on relevant populations.

Level 2: Evidence is derived from randomized controlled trials or diagnostic studies with minor limitations; overwhelming, consistent evidence from observational studies.

Level 3: Evidence is derived from observational studies (case control and cohort design).

Level 4: Evidence is derived from expert opinion, case reports, and reasoning from first principles.

The evidence was aggregated into four groups (the condition, the test, the diagnosis and the treatment) and a level of evidence quality was assigned to each group by the experts for each of the conditions. Each fact sheet includes the names of the experts who validated the data and the level of quality of the studies from which the evidence is derived.

### C. Results

Responses were received from 289 individuals, many of whom represented more than a single interest group, for a total of 582 represented areas of interest. The majority of the survey information was provided by experts in the clinical and scientific aspects of the individual conditions. The regional distribution of responses and areas of expertise of the respondents from the United States are shown in Table 3. The table also correlates the number of responses to the birth rate in each region (based on Census 2001 data). In the United States, no responses were received from the following States: Idaho, Kansas, Montana, North Dakota, South Dakota, West Virginia, and Wyoming. International responses were from Australia (4), Brazil (1), Canada (5), Chile (1), Croatia (1), Denmark (1), Finland (1), France (1), Germany (1), Italy (3), The Netherlands (1), Switzerland (1), and the United Kingdom. Most were from recognized experts in the field who were actively solicited by members of the working group for their input about specific conditions. At least three experts provided information on each condition.

Overall, a total of 3949 condition profiles were obtained. On average, seven conditions were scored per responder. Of the 84 conditions, 30 (36%) received more than 50 responses, and 5 (6%) $< 20$. The average number of profiles per condition was $47 \pm 20$; the range was 14-120. The corrected total for the 84 conditions was 3796; the number of responses for each condition is listed in Table 4. This table also shows the proportion of respondents who were unable to respond to one or more of the individual criteria and is reflected as "missing data" for each condition. This option was most frequently used in scoring criteria related to attributes of the screening test itself, with 11% of respondents not including all of the requested information.

Additional input, both domestic and international, was provided by individuals who were asked to discuss many of the broad issues under consideration by the work groups. The committee is particularly grateful for the assistance of Dr. Rodney Pollitt (Sheffield, UK), who provided insights into the system used in the United Kingdom; Dr. Adelbert Roscher (Munich, Germany), who provided insight into the recent newborn screening and MS/MS decision-making process undertaken by the German Democratic Republic; and Dr. Edwin Naylor (Pittsburgh, PA), who provided insight into the decision-making process of NeoGen Screening (now Pediatrix). In addition,

**Table 3**
Geographical distribution of respondent profiles

| | Provider screening services | | | | | | | Specialty care provider | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Region | Testing | Follow-up | Administration | Policy | Consumers | Diagnostic services | Primary care | Endocrinology | Hematology | Inf. diseases | Genetics | Inborn Errors of Metabolism | Total |
| West | 5 | 17 | 5 | 8 | 10 | 11 | 0 | 8 | 2 | 1 | 4 | 12 | 83 |
| Midwest | 8 | 23 | 4 | 16 | 14 | 20 | 1 | 5 | 2 | 1 | 12 | 18 | 124 |
| Northeast | 13 | 29 | 8 | 14 | 22 | 30 | 3 | 11 | 6 | 1 | 20 | 25 | 182 |
| South | 4 | 10 | 2 | 5 | 15 | 6 | 4 | 3 | 0 | 0 | 7 | 6 | 62 |
| Southeast | 2 | 6 | 2 | 6 | 22 | 9 | 1 | 5 | 3 | 0 | 7 | 6 | 69 |
| **Total US** | **32** | **85** | **21** | **49** | **83** | **76** | **9** | **32** | **13** | **3** | **50** | **63** | **520** |
| International | 11 | 11 | 5 | 5 | 0 | 15 | 1 | 0 | 3 | 0 | 0 | 9 | 60 |
| Not provided | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| **Total** | **43** | **96** | **26** | **54** | **85** | **91** | **10** | **32** | **16** | **3** | **50** | **72** | **582** |

**Table 4**
Survey scores of all conditions (sorted by score in descending order)

| Condition | Code | Responses | Missing data (%) | Score (sum of the means) | Rank (%ile) |
|---|---|---|---|---|---|
| Medium-chain acyl-CoA dehydrogenase deficiency | MCAD | 90 | 4 | **1799** | 1.00 |
| Congenital hypothyroidism | CH | 84 | 3 | **1718** | 0.99 |
| Phenylketonuria | PKU | 120 | 3 | **1663** | 0.98 |
| Neonatal hyperbilirubinemia (Kernicterus) | HPRBIL | 8 | 5 | **1584** | 0.96 |
| Biotinidase deficiency | BIOT | 68 | 2 | **1566** | 0.95 |
| Sickle cell anemia (Hb SS disease) | Hb SS | 55 | 8 | **1542** | 0.94 |
| Congenital adrenal hyperplasia | CAH | 93 | 7 | **1533** | 0.93 |
| Isovaleric acidemia | IVA | 53 | 3 | **1493** | 0.89 |
| Very long-chain acyl-CoA dehydrogenase deficiency | VLCAD | 58 | 2 | **1493** | 0.89 |
| Maple syrup (urine) disease | MSUD | 84 | 10 | **1493** | 0.89 |
| Galactosemia | GALT | 85 | 3 | **1473** | 0.88 |
| Hb S/ß-thalassemia | Hb S/ßTh | 43 | 8 | **1455** | 0.87 |
| Hb S/C disease | Hb S/C | 45 | 4 | **1453** | 0.86 |
| Long-chain L-3-OH acyl-CoA dehydrogenase deficiency | LCHAD | 58 | 3 | **1445** | 0.84 |
| Glutaric acidemia type I | GA I | 58 | 3 | **1435** | 0.83 |
| 3-hydroxy 3-methyl glutaric aciduria | HMG | 28 | 4 | **1420** | 0.82 |
| Trifunctional protein deficiency | TFP | 42 | 5 | **1418** | 0.81 |
| Multiple carboxylase deficiency | MCD | 46 | 2 | **1386** | 0.80 |
| Benign hyperphenylalaninemia | H-PHE | 76 | 3 | **1365** | 0.78 |
| Methylmalonic acidemia (mutase deficiency) | MUT | 60 | 2 | **1358** | 0.77 |
| Homocystinuria | HCY | 80 | 2 | **1357** | 0.76 |
| 3-Methylcrotonyl-CoA carboxylase deficiency | 3MCC | 48 | 4 | **1355** | 0.75 |
| Hearing loss | HEAR | 45 | 4 | **1354** | 0.73 |
| Methylmalonic acidemia (Cbl A,B) | Cbl A,B | 46 | 2 | **1343** | 0.72 |
| Propionic acidemia | PROP | 68 | 2 | **1333** | 0.71 |
| Carnitine uptake defect | CUD | 46 | 2 | **1309** | 0.69 |
| Galactokinase deficiency | GALK | 47 | 7 | **1286** | 0.69 |
| Glucose-6-phosphate dehydrogenase deficiency | G6PD | 42 | 5 | **1286** | 0.67 |
| ß-Ketothiolase deficiency | ßKT | 33 | 6 | **1282** | 0.66 |
| Citrullinemia | CIT | 63 | 3 | **1266** | 0.65 |
| Argininosuccinic acidemia | ASA | 60 | 4 | **1263** | 0.64 |
| Tyrosinemia type I | TYR I | 68 | 4 | **1257** | 0.63 |
| Short-chain acyl-CoA dehydrogenase deficiency | SCAD | 51 | 7 | **1252** | 0.61 |
| Tyrosinemia type II | TYR II | 57 | 3 | **1249** | 0.60 |
| Glutaric acidemia type II | GA2 | 52 | 4 | **1224** | 0.59 |
| Medium/short-chain L-3-OH acyl-CoA dehydrogenase deficiency | M/SCHAD | 21 | 11 | **1223** | 0.58 |
| Cystic fibrosis | CF | 65 | 12 | **1200** | 0.57 |
| Variant Hb-pathies (including Hb E) | Var Hb | 41 | 3 | **1199** | 0.55 |
| Human HIV infection | HIV | 29 | 8 | **1193** | 0.54 |
| Defects of biopterin cofactor biosynthesis | BIOPT (BS) | 60 | 3 | **1174** | 0.53 |

(continued)

**Table 4**
Continued

| Condition | Code | Responses | Missing data (%) | Score (sum of the means) | Rank (%ile) |
|---|---|---|---|---|---|
| Medium-chain ketoacyl-CoA thiolase deficiency | MCKAT | 23 | 13 | **1170** | 0.52 |
| Carnitine palmitoyltransferase II deficiency | CPT II | 45 | 5 | **1169** | 0.51 |
| Methylmalonic acidemia (Cbl C,D) | Cbl C,D | 45 | 4 | **1166** | 0.49 |
| Argininemia | ARG | 54 | 5 | **1151** | 0.48 |
| Tyrosinemia type III | TYR III | 42 | 5 | **1149** | 0.47 |
| Defects of biopterin cofactor regeneration | BIOPT (Reg) | 58 | 5 | **1146** | 0.46 |
| Malonic acidemia | MAL | 22 | 5 | **1143** | 0.45 |
| Carnitine: acylcarnitine translocase deficiency | CACT | 38 | 5 | **1141** | 0.43 |
| Isobutyryl-CoA dehydrogenase deficiency | IBG | 28 | 7 | **1134** | 0.42 |
| 2-Methyl 3-hydroxy butyric aciduria | 2M3HBA | 18 | 3 | **1132** | 0.41 |
| Carnitine palmitoyltransferase IA deficiency (liver) | CPT IA | 40 | 4 | **1131** | 0.40 |
| 2-Methylbutyryl-CoA dehydrogenase deficiency | 2MBG | 27 | 18 | **1124** | 0.39 |
| Hypermethioninemia | MET | 45 | 3 | **1121** | 0.37 |
| Dienoyl-CoA reductase deficiency | DE RED | 18 | 11 | **1119** | 0.36 |
| Galactose epimerase deficiency | GALE | 38 | 7 | **1066** | 0.35 |
| 3-Methylglutaconic aciduria | 3MGA | 21 | 5 | **1057** | 0.34 |
| Severe combined immunodeficiency | SCID | 69 | 6 | **1047** | 0.33 |
| Congenital toxoplasmosis | TOXO | 28 | 12 | **1041** | 0.31 |
| Familial hypercholesterolemia (heterozygote) | FHC | 25 | 2 | **1038** | 0.30 |
| Carnitine palmitoyltransferase IB deficiency (muscle) | CPT IB | 28 | 4 | **1009** | 0.29 |
| Citrullinemia type II | CIT II | 38 | 2 | **1001** | 0.28 |
| Ornithine transcarbamylase deficiency | OTC | 64 | 7 | **942** | 0.27 |
| Guanidinoacetate methyltransferase deficiency | GAMT | 23 | 1 | **922** | 0.24 |
| Wilson disease | WD | 25 | 4 | **922** | 0.24 |
| Diabetes mellitus, insulin dependent | IDDM | 51 | 16 | **891** | 0.23 |
| Neuroblastoma | NB | 14 | 4 | **864** | 0.22 |
| Arginine: glycine amidinotransferase deficiency | AGAT | 21 | 2 | **861** | 0.20 |
| Turner syndrome | TURNER | 36 | 4 | **847** | 0.19 |
| Adenosine deaminase deficiency | ADA | 20 | 4 | **841** | 0.18 |
| Carbamylphosphate synthetase deficiency | CPS | 55 | 2 | **833** | 0.17 |
| Alpha 1-antitrypsin deficiency | A1AT | 18 | 12 | **819** | 0.16 |
| Congenital cytomegalovirus infection | CMV | 18 | 12 | **779** | 0.14 |
| Duchenne and Becker muscular dystrophy | DMD | 29 | 3 | **776** | 0.12 |
| Fragile X syndrome | FX | 35 | 4 | **776** | 0.12 |
| Congenital disorder of glycosylation type Ib | CDG Ib | 34 | 5 | **766** | 0.11 |
| Smith-Lemli-Opitz syndrome | SLO | 45 | 3 | **759** | 0.10 |
| Biliary atresia | BIL | 15 | 4 | **744** | 0.08 |
| Hurler-Scheie disease | MPS-1H | 48 | 7 | **707** | 0.07 |
| X-linked adrenoleukodystrophy | ALD | 38 | 2 | **705** | 0.06 |
| Fabry disease | FABRY | 46 | 6 | **661** | 0.05 |

(continued)

**Table 4**
Continued

| Condition | Code | Responses | Missing data (%) | Score (sum of the means) | Rank (%ile) |
|---|---|---|---|---|---|
| Lysosomal storage diseases | LSD | 38 | 8 | **638** | 0.02 |
| Creatine transport defect | CR TRANS | 20 | 0 | **646** | 0.04 |
| Pompe disease | POMPE | 46 | 7 | **613** | 0.01 |
| Krabbe disease | KRABBE | 44 | 9 | **447** | 0.00 |

NOTE: Figure 5 shows the scores for all conditions that were evaluated, separated into groups based on the testing platforms (MS/MS for metabolic diseases, IEF or HPLC, for hemoglobinopathies, and all others).

several opportunities were offered for public comment over the course of these deliberations.

Based on responses to an independent survey that inquired as to the appropriateness of the criteria and the weights assigned, the expert group adjusted the scores assigned to some of the criteria. In particular, ambiguous language was clarified and a greater weight was assigned to the benefit of treatment to the infant. Scores for the parameters of the screening tests were increased to recognize the inherent value of multiplex technologies to public health.

Figures 1 and 2 display the raw data for MCAD and PKU, which were selected as representative conditions for demonstrating how the data collected for individual criteria are charted and aggregated to reach the final scores. Each respondent is listed over columns and the score offered for each criterion is shown. The sums of the mean and median scores are shown. Figures 3a through 3e display side-by-side summary data for each of the criteria used to evaluate the conditions with MCAD on the left and PKU on the right. In the top panel, the total score for each respondent is shown. The remaining panels show the scores for 18 of the 19 individual criteria (the availability of test criterion is not included) used to evaluate the conditions. The complete data in tabular form are displayed in Table 4, in which the scores are reflected as sums of the means for all conditions. The number of respondents for each condition is shown. The sums of the mean scores for all of the conditions evaluated, regardless of whether a screening test is available, are shown in Figure 4, Figure 5.

Figure 6 separates those conditions that have an acceptable, validated, population-based screening test from those lacking a test. The left side of the graph shows the conditions that have an adequate screening test currently available, while those shown on the right side lack a screening test. Among the conditions with a test, MCAD deficiency, CH, and PKU score the highest in this analysis, followed by BIOT, sickle cell anemia, CAH, isovaleric acidemia, VLCAD deficiency, MSUD, GALT, hemoglobin S/$\beta$-thal disease, hemoglobin SC disease, LCHAD deficiency, glutaric acidemia type 1, and HMG. Conditions without a test are included because they reflect the need to focus on particular aspects of the disease in order for it to be considered for newborn screening.

### D. Discussion

A number of considerations influenced the final decisions regarding which conditions should be included in a core screening panel. As previously discussed, using a two-step process, the information gathered with the data collection instrument and the review of the scientific literature provided information used to assign a score for each condition. This approach also allowed for those conditions with screening tests that have been validated in general populations to be distinguished from those conditions for which a population-based validated test was not available. The scores were first used to make some general decisions based on the highest scoring conditions. In particular, the inclusion of several conditions that are screened by either IEF or HPLC (hemoglobinopathies) and MS/MS (acylcarnitines and fatty acid oxidation disorders) led the expert group to make decisions regarding multiplex technologies and how the results should be handled. Once the conditions were separated into groups defined by either the individual condition or by the multiplex test that detects many conditions, the scoring system could be overlaid to see how conditions compare to one another within these groupings, or in total.

#### Defining and counting the conditions

Careful consideration of several factors is required to answer the seemingly basic question of how many conditions should be screened for in a newborn screening program and how they should be defined. These factors include: 1) the clinical, biochemical, and molecular complexity of the conditions under consideration; 2) the progress constantly made in our understanding of their natural history and etiology; 3) the impact of implementing multiplex platforms that allow the simultaneous detection of numerous biochemical markers; and 4) the gaps that appear to exist in the level of clinical knowledge among stakeholders involved with, or advocating for, the decision to pursue ever greater numbers of conditions. Indeed, counting has become increasingly problematic to the point that a competition seems to be taking place in which the apparent superiority of a newborn screening program or private laboratory is staked on the sole basis of quantity, with disproportionate consideration given to quality. This concept has caught the attention of the media that constantly tell the pub-

lic-at-large that the more conditions that are screened in a particular State, the better that program must be. As a direct consequence of this behavior, the number of conditions is perceived by the public and policy-makers as a scorecard, often leading to either inflated or inaccurate figures. For example, 22 States offering screening by MS/MS have included LCHAD deficiency in their panels, yet only half of the same programs claim to be screening for trifunctional protein deficiency, perhaps being unaware that the biochemical phenotype in bloodspots is essentially identical between the two conditions. Thus, the context in which screening is "quantitated" must be standardized.

This situation is not a new development brought on by modern technologies. Since the beginning of PKU screening, this has been a complex issue. The screening method for PKU led to follow-up testing to separate the patients with tyrosinemia and/or biopterin defects. Thus, many programs included tyrosine in their screened conditions, and considered biopterin defects as merely an anomaly of PKU screening that should be combined with PKU and given an asterisk when counting the number of PKU cases detected. This is hardly satisfactory when questions are asked about the incidence of the secondary targets or the outcomes of those subtypes.

When screening for sickle cell anemia became an important addition to screening panels, the singular condition of SS disease was usually counted even though the testing methodologies used could detect many different clinically significant hemoglobinopathies. Screening for sickle cell anemia progressed to screening for sickle cell diseases (SC and S$\beta$-thal) but this screening was still counted as screening for a single disorder with many other conditions detected secondarily. Further, although these are the three primary targets of hemoglobinopathy screening, the methodologies of IEF or HPLC employed in hemoglobinopathy screening can reveal over 700 variant hemoglobins, of which about 25 are considered to be of clinical significance and are reported out by some screening laboratories. Some States may only report SS disease, some SS, SC and S$\beta$-thal, and others a variable number of the other clinically significant variants. Hence, just for this one group of conditions, one can argue that a program that reports out 28 of these variants actually screens for 28 conditions. For a test involving a functional endpoint such as severe hearing loss, there are a large number of "conditions" for which the test screens.[33] There are over 77 loci for nonsyndromal hearing loss conditions, 31 loci for syndromal hearing loss conditions, as well as some of the "environmental" causes of hearing loss that would be amenable to DNA-based testing such as presence of the cytomegalovirus or other infectious agent genomes. Hence, what is considered a single condition screen, congenital hearing loss, may be considered a screen for at least 108 individual conditions at the etiologic level.

If one takes the set of conditions included in both the proposed core panel and secondary target groups, each entity reflects the significance given to a spectrum of possible criteria. In the proceedings of the working group charged with this task, choices were made to strike the best compromise between established practices, the expert opinions, and scientific evidence. In reality, counting could have been very different if this had been approached in a pragmatic way using any of the following criteria:

1. Phenotype of the condition;
2. Established groups of conditions (e.g., organic acidurias, hyperphenylalaninemias);
3. Primary marker (e.g., tyrosine, C8 acylcarnitines);
4. Test (e.g., MS/MS, IEF);
5. Response to treatment (e.g., responsiveness to cofactors, vitamins); and
6. Number of loci linked to a common phenotype (e.g., hearing loss genes as discussed above).

Table 5 shows how different "counting" could be if the criteria above were applied independently. For instance, hearing loss is a single phenotype of one group of conditions for which the primary marker is hearing loss that is detected by one test-

**Table 5**
Discrepancies in counting conditions using different criteria

| Counting conditions according to | CORE PANEL | (NOT included if overlapping with core panel) SECONDARY TARGETS | TOTAL |
|---|---|---|---|
| Clinical phenotype (1) | 27 | 14 | 42 |
| Established groups of conditions (2) | 10 | 0 | 10 |
| Primary marker (3) | 22 | 29 | 51 |
| Test platform (4) | 9 | 2 | 11 |
| Response to treatment (5) | 32 | 14 | 46 |
| Number of loci (6) | 142 | 28 | 170 |
| Expert group (7) | 29 | 25 | 54 |

(1)All clinical subsets (e.g., severe, mild) considered as a single entity.
(2)Organic acids disorders, hemoglobinopathies, endocrine disorders.
(3)Analyte with best sensitivity and specificity (e.g., C8 for MCAD or phenylalanine for the hyperphenylalaninemias).
(4)Either singleton test or multiplex platform count as one.
(5)Significant in a few cases (e.g., responsive versus non-responsive forms to a particular treatment).
(6) Based on OMIM (), with modifications.
(7)Selected from a total of 84 conditions.

ing platform, audiometry. The single response to treatment for the group is improved hearing or communication. However, as previously discussed, there are at least 108 genes for conditions associated with hearing loss. Similarly, while C8 is a primary marker of MCAD, it's also a primary marker for GA-II, M/SCHAD and MCKAT. It is detected in a single multiplex platform, MS/MS. Treatments are similar but as indicated above, and multiple conditions are associated with the marker.

It is evident that quantitation and categorization of newborn screening disorders remains imperfect and inconsistent and that, until standardized, there will continue to be confusion about the extent of screening in individual programs and the nation. The expert panel recognizes these disparities and their rationale, and recommends the implementation of a standardized and common nomenclature for an objective and scientifically sound description of the screening test panel being offered and the reporting of results. Such a classification system would require some consensus among the newborn screening and subspecialty communities, but should be possible. Standardization of panels, and consistent screening methods and case definitions will allow more pooling of available data on the utility of screening.

**Integrating the evidence base with the survey results**

Information obtained from the scientific literature and the surveys was used to create the fact sheets that were developed for each condition (see Appendix 1). The fact sheets are structured to provide summary information describing:

1. The type of condition;
2. The test;
3. The extent to which United States newborns are being screened for the condition;
4. Whether there is apparent ethnic variability in incidence;
5. The number of individuals providing information on the condition;
6. The proportion of scores from survey respondents considered valid; and
7. Citations in PubMed as of February 2004.

Information obtained from the surveys is shown on the left side of the first page. The percent of maximum score of the survey respondents is shown next to each criterion. The data from the two criteria for which there was the lowest correlation among respondents is also shown on the left side of page 1. The evidence from the literature is shown on the right side of the first page. Additional summary information including the scores (maximum of 2,100) is shown along with an assessment of whether the data from the surveys are consistent with the evidence from literature. Significant discrepancies are discussed in the comment box. Although the language of the criterion is often not identical to that expressed in the literature, there was significant correlation between the survey results and the evidence from the literature. The fact sheets for all other conditions evaluated are provided in Appendix 1.

**Influence of testing technology**

New technology has been one of the driving forces in the evolution of newborn screening programs in the United States and is a critical factor in the evaluation of a condition to determine how appropriate for screening it is. Typically, determining the appropriateness of newborn screening was based on the conditions themselves and their associated testing methods. However, new technologies often raise questions that have not yet been addressed. Multiplex methods such as genomic arrays require that the sequence tested deliberately be placed in the array. This is distinct from technologies that look globally at a class of molecules, for example, IEF or HPLC that reveal all hemoglobin variants, or an MS/MS run to detect acylcarnitines that reveal compounds in the C2 through C18 range. Complicating the use of MS/MS is the fact that many of the compounds identified are associated with more than one condition and these conditions may not have similar clinical and laboratory features. Thus, the criteria used to judge whether to include a condition in a newborn screening panel will vary among the conditions. It becomes difficult to compare a condition that has a unique test/technology that tests only for the condition of interest to a technology that can detect many conditions, some of which are related through their differential diagnosis, while others involve independent compounds in the MS/MS profile. The use of MS/MS for acylcarnitines, for example, differs from its use for detection of amino acid disorders in which there is little overlap between the analytes associated with the conditions. Table 6 shows the relationships between analytes for high scoring conditions and those of lower scoring conditions.

Independent decisions were made about conditions screened using MS/MS and HPLC or IEF for hemoglobinopathies. One reason is that among the acylcarnitine disorders there is little differentiation between the highest and lowest scoring conditions. For many conditions, the difference is accounted for by differing incidence figures—a criterion that loses some of its importance when the test for the more common conditions also can detect less common conditions.

It is important to note that two approaches are currently being used in screening with MS/MS. A majority of screening laboratories now run full profiles that allow them to visualize the full range of acylcarnitines or amino acid compounds. However, a minority operate their systems in a selective reaction monitoring (SRM) mode, which allows them to obtain results only on the subset of compounds that are associated with those conditions that are being targeted in the screening programs. Some programs use a combination of SRM and profiling with either approach, the screening test is driven more by analytes than by the conditions with which they are associated. An assessment of the advantages and disadvantages of the test results for each approach led to an expert group preference for the full-profile approach for four reasons.

First, in reviewing those acylcarnitine-associated conditions that were high scoring in this analysis (MCAD, IVA, VLCAD, LCHAD, GA1, HMG and TFP) (see Table 4), it was apparent

**Table 6**
Differential diagnosis between core panel and secondary target conditions

| PRIMARY TARGETS | | SECONDARY TARGETS |
|---|---|---|
| **Higher Scoring** | **Lower Scoring** | |
| MCAD | | GA2<br>M/SCHAD<br>MCKAT |
| PKU | | H-PHE<br>BIOPT (BS)<br>BIOPT (REG) |
| Hb SS | Hb S/ß-Th<br>Hb S/C | VAR Hb |
| IVA | | 2MBG |
| VLCAD | LCHAD<br>TFP | CPT II<br>CACT |
| GALT | | GALK<br>GALE |
| BIOT (*) | MCD<br>PROP | |
| MUT | Cbl A,B | Cbl C,D |
| HCY | | MET |
| HMG | 3MCC<br>BKT | 2M3HBA<br>3MGA |
| CUD | | CPT IA |
| CIT | ASA | CIT II |
| TYR I | | TYR II<br>TYR III |

NOTE: Codes are as listed in Table 2. A differential diagnosis is required between conditions listed in the same row. (*) indicates that biotinidase deficiency is occasionally diagnosed by MS/MS.

that several acylcarnitines must be analyzed in order to maximize assay specificity and sensitivity. A majority of the remaining conditions detected by MS/MS were also included in the differential diagnoses of the higher scoring conditions. Thus, screening for a core set of conditions ultimately results in screening for a much wider range of conditions.

Second, the use of MS/MS profiles allows for the maximal use of the technology for the identification of clinically significant conditions.

Third, the use of MS/MS profiles offers better quality control of preanalytic and analytic aspects of testing. Allowing all information to be assessed can reveal the presence of spurious signals and/or contaminants in the specimens or reagents and devices used in the test system.

Fourth, the use of MS/MS profiles enhances clinical interpretation of results by revealing anomalies in associated compounds or in compounds that provide internal standards against which excesses or deficiencies can be better interpreted. Hence, the expert group recommends that a full MS/MS profile should be analyzed, and any clinically significant results should be reported by the laboratory to the health care provider and family of the infant. Some of the conditions detectable by acylcarnitine profiling may turn out to be benign in a number of cases (i.e., SCAD, 2MBCAD, and 3MCC). The secondary conditions detectable by a multiplex technology such as MS/MS or HPLC and included in a differential diagnosis for the primary target conditions can be screened at minimal additional cost and are, in fact, determined in the diagnostic setting during follow-up. There could be additional cost associated with diagnosis and follow-up, although many of these cases would be detected clinically after birth and higher costs would inevitably be incurred by the health care system and the family, although not as a result of the newborn screening program.

The expert group also devoted considerable discussion to the question of how best to present the results of analyses of conditions. As previously discussed, the lists of conditions used are inherently longer than the lists many States use to describe the newborn screening tests they offer because the expert group chose to break down the heterogeneity of conditions by listing them by etiologic type or by the analytes associated with the conditions. It would be inappropriate to consider this list of conditions as a scorecard for the number of conditions screened. It is only by considering each condition in each of its etiologic forms that a direct analysis can be done.

In the following section, diseases are assigned to categories as a means of conducting the analyses (see Tables 7 and 8). The main category, referred to as the core panel, includes those conditions considered appropriate for newborn screening. The 29 conditions in this core panel are similar in that they all have:

1. Specific and sensitive screening tests;
2. A sufficiently well understood natural history; and
3 Available and efficacious treatments.

**Table 7**
The core condition panel

| MS/MS | | | | |
|---|---|---|---|---|
| Acylcarnitines | | Amino acids | | |
| **9 OA** | **5 FAO** | **6 AA** | **3 Hb Pathies** | **6 Others** |
| **CORE PANEL** | | | | |
| IVA | MCAD | PKU | Hb SS* | CH |
| GAI | VLCAD | MSUD | Hb S/ß-Th* | BIOT |
| HMG | LCHAD | HCY* | Hb S/C* | CAH* |
| MCD | TFP | CIT | | GALT |
| MUT* | CUD | ASA | | HEAR |
| 3MCC* | | TYR I* | | CF |
| Cbl A,B* | | | | |
| PROP | | | | |
| BKT | | | | |

Codes are as listed in Table 4. OA, disorders of organic acid metabolism; FAO, disorders of fatty acid metabolism; AA, disorders of amino acid metabolism; Hb Pathies, hemoglobinopathies. (*) See individual condition discussions.

**Table 8**
The secondary target condition panel

| SECONDARY TARGETS | | | | |
|---|---|---|---|---|
| **6 OA** | **8 FAO** | **8 AA** | **1 Hb Pathies** | **2 Others** |
| Cbl C,D* | SCAD | HYPER-PHE | Var Hb* | GALK* |
| MAL | GA2 | TYR II | | GALE |
| IBG | M/SCHAD | BIOPT (BS) | | |
| 2M3HBA | MCKAT | ARG | | |
| 2MBG | CPT II | TYR III | | |
| 3MGA | CACT | BIOPT (REG) | | |
| | CPT IA | MET | | |
| | DE RED | CIT II | | |

Codes are as listed in Table 4. OA, disorders of organic acid metabolism; FAO, disorders of fatty acid metabolism; AA, disorders of amino acid metabolism; Hb Pathies, hemoglobinopathies. (*) Identifies conditions for which specific discussions of unique issues are found in the main report.

The expert group concluded that conditions with evidence-validated scores equal to or above 1,200 meet these key criteria and should be considered appropriate for newborn screening.

Analysis of the distribution of scores among the conditions in Figure 7 shows that around a score of 1,250, one moves into a group of conditions that are part of the differential diagnosis of higher scoring conditions, but for which natural history is less well understood or efficacious treatment is lacking. These conditions occupy the middle third of the curve. CF (1,200) is the only condition currently screened that scores in this range but is not part of the differential diagnosis of a higher scoring condition. (Its lower score may reflect the ongoing debate about the benefits of screening for CF, despite the evidence for screening and the lack of evidence of significant harms from screening.)[34–35] Otherwise, all conditions in this middle third scoring between tyrosinemia type I (score = 1,257; 63rd centile) and galactose epimerase deficiency (score = 1,066; 35th centile) are part of the differential diagnosis of another higher scoring condition. The expert group recognizes that it is difficult to draw a line in a continuum that would reasonably discriminate between groups of conditions. Programs should appreciate that scoring cut-offs may have wide and varying confidence limits due to differences in numbers of responders. The final scores represent a rough relative approximation of ranking of disorders and serve only as an initial step to guide decision-making; analysis of the evidence base for the score needs to be included in the decision-making process.

Conditions then were redistributed between the core panel and the secondary target category on the basis of the evidence related to the availability of an efficacious treatment and a well understood natural history. Other conditions were moved from the "not appropriate for newborn screening category" to secondary targets if they were revealed by the multiplex technology used to identify core panel conditions. SCAD, IBG, ARG and DE RED were moved into the secondary target category on this basis. Among conditions initially placed in the core panel category on the basis of the survey score, CPT-II was shifted to the secondary target category on the basis of the lack of a proven efficacious treatment. Several conditions were moved to the secondary target category on the basis of scientific evidence indicating that the natural history was not sufficiently well understood. These include TYR-II, GA-2, and M/SCHAD. GALK deficiency was moved to the secondary target category on the basis of the relatively limited burden of disease and the fact that a second test is usually required to screen for the condition. G6PD was moved to the category of conditions not recommended for newborn screening because of a limited knowledge of the natural history of the mutations in the G6PD gene found in the United States. There is also limited knowledge of the implications of these mutations with regard to development of severe hemolytic disease in the United States population. Additionally, because G6PD is not identified in the course of screening for other core conditions, it was not placed in the secondary target category. Finally, a subset of conditions was identified for which carrier status could be established on the basis of the screening test result and for which reporting is considered appropriate. These include MCAD, VLCAD, Hb-pathies, 3MCC, CUD, and CF.

The next group of conditions includes those that are clinically significant and are part of the differential diagnosis of a condition listed in the core panel or that are revealed through a multiplex technology. Note that secondary hemoglobinopathies are revealed in the screening laboratory while most others are revealed in the diagnostic setting during follow-up. Table 8 lists the conditions in this secondary category. Table 5 shows the relationships among many of the core conditions and the conditions included in their differential diagnoses (or secondary targets). In particular, some of the metabolic conditions in this group are characterized by having a sensitive and specific test, but a deficiency in the availability of an efficacious treatment or limited knowledge of the natural history of the condition, although there may be sufficient knowledge to justify the reporting of test results to the family and health care provider of the infant.

The recommendation to report all clinically significant results is an approach similar to that taken for hemoglobinopa-

thy screening, in which a core set of conditions is screened. The technologies of choice in many laboratories for hemoglobinopathy screening are IEF and HPLC, which can detect the full range of more than 700 hemoglobin variants, including those in the core panel, for which clinically significant variants are reported.[36] By handling hemoglobinopathies in a way similar to the acylcarnitine and amino acid disorders screened for by MS/MS, the expert group was left with a much smaller group of conditions to consider independently for screening suitability. These conditions have adequate screening tests and efficacious treatments, but they are detected by methods other than MS/MS, and usually as singleton tests.

Table 9 lists the conditions that were determined to be without a screening methodology that has been adequately validated for general population-based screening. Kernicterus risk as determined by the identification of hyperbilirubinemia stands out in this group as being a very high scoring condition.

Figure 8 shows the distribution of conditions into the: core panel (29 conditions); secondary target category (25 conditions); no test available (23 conditions), those excluded from newborn screening categories due to other inadequacies in meeting the criteria (4 conditions), and the three conditions on which we deferred decision-making.

**Table 9**
Conditions for which Newborn Screening is NOT Indicated at this Time

| | MS/MS | | | | |
|---|---|---|---|---|---|
| | Acylcarnitines | | Amino acids | | |
| | OA | FAO | AA | Hb Pathies | Others |
| No Test | | | | | |
| | | CPT-1B | OTC | | HPRLBIL |
| | | | CPS | | FHC |
| | | | | | SCID |
| | | | | | IDDM |
| | | | | | GAMT |
| | | | | | WD |
| | | | | | AGAT |
| | | | | | NB |
| | | | | | TURNER |
| | | | | | BIL |
| Excluded | | | | | |
| | | | | | ADA |
| | | | | | A1AT |
| | | | | | DMD |
| | | | | | G6PD* |
| Deferred | | | | | |
| | | | | | HIV |
| | | | | | TOXO |
| | | | | | CMV |
| | | | | | FX |
| | | | | | CDG-1b |
| | | | | | SLO |
| | | | | | ALD |
| | | | | | MPS-1H |
| | | | | | FABRY |
| | | | | | CR TRANS |
| | | | | | LSD |
| | | | | | POMPE |
| | | | | | KRABBE |

Codes are as listed in Table 4. OA, disorders of organic acid metabolism; FAO, disorders of fatty acid metabolism; AA, disorders of amino acid metabolism; Hb Pathies, hemoglobinopathies. (*) Identifies conditions for which specific discussions of unique issues are found in the main report.

### Selected condition discussions

The following conditions represent a group for which there was either deviation from the adopted data processing plan or for which unusual issues justify additional discussion. It is important to realize that the data on the laboratory sensitivity and specificity of many conditions identified by MS/MS is suboptimal, though it was sufficient to lead the expert group to classify them as it has done.

### Congenital Adrenal Hyperplasia (CAH)

Table 7 CAH includes a number of forms of the disease. The most common is 21 hydroxylase (21-OH) deficiency, which accounts for 95% of cases and is the general form that has been considered. The primary marker used in newborn screening for 21-OH, 17-hydroxyprogesterone (17-OHP), is most sensitive in identifying infants with the severe salt-wasting form in which elevations are very high. The degree to which 17-OHP is elevated in the nonsalt-wasting forms is variable. Hence, sensitivity in detecting this form by newborn screening is reduced. The 21-OH forms of CAH were not subdivided as were the hyperphenylalaninemias because the forms of 21-OH are caused by the same gene. However, many programs consider the identification of newborns with the nonsalt-wasting form to be a by-product of screening for the primary target, the salt-wasting form. In the salt-wasting form, most virilized females should be clinically detectable because of "ambiguous genitalia" or as virilized females. However, it is important to identify the males by screening to prevent early morbidity and mortality. The other CAH types found in the remaining 5% of patients are not detectable generally by current screening strategies.

### Galactokinase Deficiency (GALK)

Table 8 Galactokinase deficiency scored 1,286 points in the analysis. However, the only consistent phenotype is cataracts. Further, in order to screen for GALK, an additional test is required. Most screening laboratories include a combination of the Beutler fluorescent spot screening test and a fluorometric or bacterial inhibition assay for total galactose. Because GALK is very rare and is part of the differential diagnosis of GALT, it has been designated as a secondary target.

### Glucose 6-Phosphate Dehydrogenase Deficiency (G6PD)

Table 9 G6PD deficiency is included in newborn screening programs in some countries, particularly in Asia and the Mediterranean, where it is the most common enzymopathy. Newborn screening programs in the Philippines and in Taiwan have reported incidence figures of 1 in 65. In the United States, G6PD screening is provided as part of the screening panel for the District of Columbia – the only program to mandate and provide screening for G6PD deficiency (Missouri has mandated G6PD screening but has not yet implemented the screen-

ing). The vast majority of the clinical data are from countries in which the risk factors (e.g., ingestion of fava beans, infections, and drugs such as sulfonamides and antimalarials) associated with G6PD status are more common and in which the prevalence is higher (e.g., tropical Africa, Middle East, tropical and subtropical Asia and in some areas of the Mediterranean). There is very limited data available from any screening program in the United States, and the opinion of hematology experts is that the variants that exist in the United States African American population are clinically benign unless the individual is in a severely compromised (i.e., oxidized) state, usually resulting from drug exposure./ Additional data are needed from programs now screening for G6PD before this condition can reasonably be considered for inclusion in a mandated core panel of screening conditions. Programs currently screening for G6PD are encouraged to collect and publish the data for determining clinical relevancy and analytical specificity and sensitivity of tests being used. Further, and as discussed below in the context of hyperbilirubinemia, some conditions are not mutually exclusive. Appropriate monitoring and management of jaundice could identify those cases at risk for Kernicterus or biliary atresia.

### Hemoglobinopathies (Hb Pathies)

Table 8 Hemoglobinopathies are screened by HPLC or IEF in most programs. The primary focus of the review of scientific literature was on sickling disorders, since they have been the primary targets of newborn screening. However, there are over 700 hemoglobin variants identified by the methods used for screening, and 25-30 are considered clinically significant. Many of these conditions are associated with an Hb SS allele, but not all. Among these variant hemoglobinopathies, Hb E is by far the most common. The expert group agreed with the current recommendations that all clinically significant hemoglobinopathy variants be reported to health care professionals. It is appreciated that there may be conditions that occur more commonly in subpopulations, such as the case of Hb E in the Hmong population, and that may alter local screening practices.

### Homocystinuria (HCY)

Table 7 Homocystinuria is screened for by detection of an elevated concentration of methionine, a secondary biochemical marker of the condition. The differential diagnosis of HCY includes other defects of methionine metabolism, unrelated liver disease, common dietary artifacts (total parenteral nutrition), and analytical issues (lability of methionine internal standard).[37] Hence, screening for HCY has a lower sensitivity than other amino acid disorders included in the core panel, and requires special attention in result interpretation to minimize the rate of false positive results. Although a primary screening based on methionine is less than ideal, the identification of newborns with a potentially treatable condition was a determining factor for the high score assigned to HCY in the survey and its inclusion in the core panel. This situation is likely to evolve when a second tier test capable of measuring total homocysteine in bloodspots becomes routinely available by MS/MS or other methods; an improvement that will strengthen the inclusion of HCY in the core panel.

### Hyperbilirubinemia (HPRLBIL)

Table 9 Based on the responses of seven experts asked to complete the data collection instrument, this was among the highest scoring conditions. However, the expert group determined that there was not a screening methodology that was sufficiently well validated in a large newborn population to justify mandated universal screening at this time. Although bilirubin test result nomograms have been validated in smaller studies, the current nomograms are not sufficiently reflective of the broad population. There are also risk factors for hyperbilirubinemia associated with other conditions such as G6PD deficiency that are assessed independently. Additionally, in order for bilirubin to be used as a marker of this condition, a specimen would have to be taken and testing would likely have to occur in the local nursery, because results would need to be rapidly available based on current understanding of hyperbilirubinemia. Therefore, the question is raised whether this should be a mandated newborn screen or, rather, be instituted as an appropriate standard medical practice for any newborn.[38] Currently, universal testing for hyperbilirubinemia is not routinely conducted in most hospitals.

### Methylmalonic Acidemia

Methylmalonic acidemia (MMA) exists in several etiologic forms caused by defects of either the apoenzyme (MMA-CoA mutase) or the biosynthesis of the coenzyme (adenosyl-cobalamin). The forms associated with a coenzyme defect may overlap biochemically with acquired dietary deficiencies. The biochemical marker of MMA is propionylcarnitine. Overall, there is credible evidence of less than ideal sensitivity with the current testing technology (affected cases with normal concentration when tested at birth) and specificity (relatively high rate of false-positive results, including cases with relatively high levels that are followed up by perfectly normal plasma acylcarnitine and urine organic acid profiles). It is likely that the introduction of a second-tier test capable of measuring methylmalonic acid in bloodspots could improve the sensitivity and specificity of newborn screening for MMA and reinforce the inclusion of this condition in the core panel. Because newborn screening is considered a program that extends beyond the screening test itself, it was decided that the disorders characterized by an elevated propionylcarnitine (mutase deficiency, cobalamin A, B, C, and D deficiencies, as well propionic acidemia) should be subdivided, particularly since they have quite different natural histories and treatment options.

### 3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC)

Table 7 The natural history of 3MCC has been driven by the clinical ascertainment of patients presenting with severe acute episodes. However, since newborn screening with MS/MS began, several individuals have been identified with the analytes associated with the condition but without apparent clinical

manifestations. This situation includes cases where the abnormal metabolites found in the neonatal bloodspot were of maternal origin, subjects who are usually biochemically affected but symptom-free. All elements being considered, it is in the best interest of newborns affected with 3MCC that the condition be identified in all cases. 3MCC was therefore included in the core screening panel with the expectation that long term follow-up will lead to a better understanding of this condition and its clinical significance.

### Tyrosinemia Type I (TYR I)

Table 7 TYR I is a condition caused by fumarylacetoacetate hydrolase deficiency that presents with severe liver and renal disease and peripheral nerve damage. If left untreated, most patients die of liver failure in the first years of life. Treatment with the drug NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3,-cyclohexanedione), diet, and liver transplant are now considered to be very effective. Newborn screening is based on the detection of an elevated concentration of tyrosine. There is evidence of less than ideal sensitivity with the current testing technology (affected cases with normal concentration when tested at birth) and poor specificity (very high rate of false positive results, mostly premature babies and newborns with liver disease of variable etiology). Although the introduction of a second-tier test capable of measuring succinylacetone in bloodspots could improve the sensitivity and specificity of newborn screening for TYR-I, the question of whether affected but asymptomatic newborns are being identified with any degree of consistency remains to be answered. It is a general and accepted concern that hepatorenal tyrosinemia may not be detected by MS/MS analysis of tyrosine concentration alone. However, TYR-I is included in the core panel for historical reasons and because of the effectiveness of treatment. It remains important not to exclude the diagnosis of tyrosinemia on the basis of a screen negative result.

### Limitations of methodology

Over the course of this project a number of limitations became apparent. Conditions with limited available evidence reported in the scientific literature were more difficult to score and place in one of the three categories. Some conditions had been reported in 10 or fewer families in the world, and for other conditions, there were gaps in the evidence base in the literature. Many conditions were found to occur in multiple forms distinguished by age-of-onset, severity, or other features. In most cases, decisions related to newborn screening were based on the more severe and treatable forms of the conditions.

The knowledge base about genetic diseases grows through a common pathway and, unless a condition was already included in newborn screening programs, there was a potential for bias in the information related to some criteria. The most severe forms of genetic diseases are usually those first noted. As one moves into the families of these probands, this bias toward severity is reduced. However, it is not until a large general population has been studied that the true performance characteristics of the various screening tests are appreciated. Because many of the conditions under consideration are very rare and the genetic etiologies may vary by ethnicity and other parameters, a population of considerable size is required to acquire a broad understanding of the condition.

Due to the aforementioned limitations, expert opinion that considered reasoning from first principles and the quality of the studies underlying the data contributed significantly to the placement of the conditions into particular categories.

Numerous barriers to implementing an optimal screening and follow-up program were identified. Recommended actions to overcome these barriers include the establishment of a national role in scientific evaluation of conditions and the technologies by which they are screened, standardization of case definitions and reporting procedures, enhanced oversight of hospital-based screening activities, long-term data collection and surveillance, and consideration of the financial needs of programs to allow them to deliver the appropriate services to the screened population.

Finally, there were limitations in both time and resources available to accomplish a project as broad and comprehensive as this. A large number of conditions commonly managed by differing subspecialists were assessed and, due to their rarity, it was not unusual that there may only be a handful of acknowledged experts of particular conditions in the world. It was also necessary to include a significant number of experts not directly involved in the expert group or its work groups. In order to broaden the number of individuals from whom we might draw for assistance with data collection and validation, it was necessary to consult with international experts.

In many ways, the analyses done under this project provide a current snapshot of the knowledge base from which recommendations are drawn. Decisions were made as to the adequacy of the evidence on which the recommendations are based. However, as is common for rare diseases, the acquisition of new knowledge is ongoing and long-term surveillance is needed to ensure that the evidence continues to support the recommendations.

### Decision making for conditions being evaluated

A primary consideration in evaluating conditions is the availability of the test. The parameters that determine "availability" are numerous and vary considerably among conditions. It is also difficult to compare tests because of the differing "value" of a technology (e.g., multiplex capability, appropriateness of the site to conduct the screening service). The expert group considered whether the tests are amenable to a screening laboratory; for example, some tests are functional, such as those for hearing screening, and must be performed in the nursery. Other tests may have significant time constraints and are therefore better conducted in the hospital or birthing facility laboratory, as would likely be the case for bilirubin screening for kernicterus risk. It also should be noted that some of the conditions considered by the expert group did not meet the criterion that the test must be performed in the 24- to 48-hour period after birth (e.g., Wilson disease, familial hypercholes-

terolemia, Duchenne muscular dystrophy, congenital disorders of glycosylation, Turner syndrome screened by FSH levels). However, such conditions may be appropriate for screening at a later time in infancy or later in childhood. Although early and continuous screening of infants and children is a critical public health goal—as is lifelong screening—the expert group analysis was limited to conditions that should be and could be evaluated some time within the first few days of life. For the most part in the United States, the focus of traditional newborn screening programs has been on disorders detectable in the first 12 to 48 hours prior to discharge from the nursery. As such, the analyses were all predicated on testing done during this time frame. Initial screens in the neonatal period (i.e., first 28 days of life) would constitute a separate program with different costs and yields of cases and therefore should be separately analyzed.

Within this framework, the basis for decision-making as shown in Figure 9 starts with whether a screening test is available, a criterion without which decisions to screen cannot be made. Clearly, the first decision to screen is based on the availability of a sensitive and specific screening test that can be done in the 24- to 48-hour interval after birth. However, there is occasional disagreement as to whether a test is adequately validated for use in general populations. Hence, survey respondents may not necessarily give a 200-point score but may give a score between zero and 200. We defined the existence of the screening test as corresponding to a score between 100–200 points. Conditions determined to have a screening test are then evaluated with respect to the criteria.

Understanding that the evidence for each criterion needs to be evaluated, conditions with validated scores, scoring above 1,200 are considered appropriate for inclusion as primary targets in a screening program. However, the expert group distinguishes between those that are primary target conditions and those that are included in the differential diagnoses for those primary target conditions. Those with tests available and scoring between 1,000 and 1,200 are secondarily reconsidered as to whether an efficacious treatment is available and, if so, they are then reconsidered as to whether the natural history of the condition is well understood. If one of these is answered "no" but the condition is part of the differential diagnosis of a core condition, it is placed in the secondary target category. If it is not part of the differential of another core panel condition, the condition would not be considered appropriate for newborn screening at this time. Conditions falling between 1,000 and 1,200 are also considered appropriate for the secondary target category while those with an overall score under 1,000 are not considered appropriate for newborn screening at this time. At the bottom of the algorithm, the expert group acknowledges that there are currently significant research studies and clinical trials in process involving screening tests and therapeutics for diseases that might make the condition amenable to newborn screening (e.g., lysosomal disorders). The information that determined the current recommendation of the expert group is not static. Conditions not considered appropriate for the core panel at this time should be reevaluated periodically to determine if their status has changed.

The data collection instrument used in this project provides information on only one aspect of a broader decision-making process required for evaluating conditions and establishing a uniform newborn screening panel (see decision tree in Fig. 9). There are also features of tests, such as costs, that are not factored into this diagram that State newborn screening programs may take into account. The algorithm can be used prospectively as a tool to evaluate conditions for their appropriateness for addition to or removal from a screening panel (Appendix 2). Reference information about each condition the expert group evaluated and the summary information can be compared to the results of an independent assessment of a condition. Review of the scientific literature should be conducted and expert opinion should be gathered for any condition evaluated. The preference is to use data from the literature. For the most subjective criteria, expert opinion is supplemented with the views of individuals involved with newborn screening programs and child health professionals and families.

**Reporting responsibilities**

Many factors affect the decisions about reporting of individual test results made by laboratories and programs. Some State newborn screening programs report directly to child health professionals, while others report to designated subspecialists. Some also report test results to families. Reporting also varies according to whether the results are screen-positive or screen-negative. As noted earlier, all results of likely clinical significance that are apparent in the testing platforms targeting specific conditions should be reported. As recommended by the Sickle Cell, Thalassemia and Other Hemoglobin Variants Subcommittee of CORN (1995), each screening program should develop guidelines for follow-up of carriers of all clinically significant conditions. This currently includes hemoglobinopathies and also would now apply to CF, because for both conditions the primary- or second-tier tests reveal carrier status. Similarly, second-tier testing for molecular causes of MCAD and other disorders can lead to the identification of carriers of the conditions (for autosomal recessive disorders). The differences in expectations between the conditions in the core panel and those in the secondary target category should be noted. Inherent to conditions in the core panel is the need to maximize detection in screening while minimizing excessive false positives being referred into the health care system. For conditions in the core panel that are positive on screening due to specific analytes being elevated, the secondary targets are identified in the diagnostic laboratory. It was on the basis of firm knowledge about these conditions that most decisions were made. The identification of conditions in the secondary target category is based on the fact that results are available due to the multiplex or multianalyte nature of the screening technology used. However, it does not presume that screening tests have been maximized for the detection of these conditions or that the knowledge base is sufficient to have developed an expectation of maximum health outcomes following interventions.

Newborn screening program officials also make decisions about following patients after initial screening and reporting. For instance, false-positives are treated as true positives until proven otherwise. However, once shown to be a real false-positive result, the State newborn screening program often treats the infant as they would a screen-negative infant, without pursuing further follow-up. The expert group believes that this situation warrants additional postconfirmation decision-making but acknowledges that the programs must minimally understand final diagnoses in order to discriminate false-positives from real-positives for these "secondary" targets.

State programs must decide whether the individual prevalence, costs and burdens of identifying these additional diseases—which may not be treatable and may take resources away from the treatable diseases originally targeted through these programs—can justify their inclusion in the program. They also must take into consideration the issues raised by child health professionals who will receive results about very rare conditions about which they have limited knowledge. Regardless of whether the State newborn screening program chooses to integrate secondary target cases into their full newborn screening program, it is important that an organized system of data collection and surveillance be available. The issues in newborn screening are similar to those that the FDA has faced with therapeutics for rare diseases, in which a shift toward phase IV (postmarket) surveillance during clinical trials has emerged. This shift recognizes that the most critical data about genetic diseases arise in the context of full population analysis. However, clinical data about the "normal" population is very scarce because the research focus has been on those with disease and on the diseases themselves. The significant variability inherent in genetic diseases requires significant knowledge of the expression of genetic variants in a general population before they are well understood. Such data collection has not been a priority of funding agencies.

### E. Summary

Significant variability exists in the types of newborn screening available and the conditions screened across the United States. This project was intended to evaluate the scientific and medical evidence in order to identify conditions appropriate for newborn screening. After articulating overarching principles to guide decision-making, the current practices and systems in the States/regions and other countries were assessed.

All analyses were done from the perspective of national data, since one of the goals of the project was to bring standardization and uniformity to newborn screening. It is appreciated that some conditions may occur more commonly in subpopulations, such as is the case for IBG and HbE in the Hmong population, and that that may alter local screening practices.

Criteria were defined that would be used to compare the many conditions under consideration. The scientific literature related to each criterion was reviewed for each of 84 conditions and the opinions of at least three acknowledged experts for every condition was evaluated. At the first level of analysis, an assessment was made as to the availability of a screening test that had been validated in a large general population. Scores were then established for each condition and they were assigned to one of three groups:

1. Core Panel (shared in common a high score [≥1,200], the availability of an efficacious treatment, a knowledge of natural history adequate for inclusion in a public health screening program);
2. Secondary Targets ([1,000–1,200] conditions that are part of the differential diagnosis of a core panel condition); and
3. Not Appropriate for Newborn Screening ([<1,000] either no newborn screening test is available or there is poor performance with regard to multiple other evaluation criteria).

The scientific evidence was overlaid on an initial categorization of conditions to ensure that all conditions in the core panel had a sufficiently well understood natural history and that an efficacious treatment was available.

The expert group recommends that State newborn screening programs:

1. Mandate screening for all core panel conditions defined by this report;
2. Mandate reporting of all secondary target conditions defined by this report and of any abnormal results that may be associated with clinically significant conditions. Some are identified in screening laboratories (e.g., hemoglobinopathies) and others in the diagnostic laboratory (e.g., MS/MS screened conditions). Clinically significant conditions also include the definitive identification of carrier status;
3. Maximize the use of multiplex technologies; and
4. Consider that the range of benefits realized by newborn screening includes treatments that go beyond an infant's mortality and morbidity.

## SECTION II: THE NEWBORN SCREENING SYSTEM: PROGRAM EVALUATION, COST-EFFECTIVENESS, INFORMATION NEEDS, AND FUTURE NEEDS

### A. The newborn screening system

In order to successfully expand the number of mandated disorders screened for in newborns, the full breadth of the screening process and its components must be fully operational. Thus the expert group and its Diagnosis and Follow-up Work Group sought to examine the current status of screening systems throughout the United States, with particular attention paid to the diagnosis and follow-up components and their interface with the newborn screening program and primary health care professionals. In addition, the group was interested in identifying the key components of screening and highlighting some best practices that appear to improve outcomes. The six components of the newborn screening process that were assessed are:

1. Education, including prenatal education;

2. Screening, including specimen collection and testing;
3. Follow-up, including result reporting;
4. Diagnostic confirmation;
5. Management; and
6. Program evaluation and continuous quality improvement.

Much of the information reported in this section was obtained from a survey of State newborn screening programs conducted by the NNSGRC and reported at a November 2002 meeting sponsored by HRSA/MCHB and University of California, Los Angeles (UCLA), entitled "Educating Parents and the Informed Decision-Making Process Regarding Newborn Screening Procedures and the Use and Storage of Residual Bloodspots." NNSGRC has updated this information through June 2004.

**Education**

As screening increases there is a growing need for education across all groups of constituents, including parents and guardians, obstetrical providers, infants' medical homes, pediatric specialists, and emergency room/labor-delivery/neonatal intensive care unit (NICU) staffs. Education should occur in several places and times in the screening system, appropriate to the needs of patients, families, and health professionals.

Newborn screening programs typically provide educational materials during the perinatal period. The materials include information about newborn screening in general and brief descriptions of the conditions that are screened. Nineteen of 50 programs indicated that distribution of their newborn screening brochures was mandatory in birthing hospitals. Only one program reported not having an informational newborn screening brochure. All but three of the 50 programs indicated that their brochures included a list of disorders screened, and all but two described the specimen collection procedures and timing. Twenty provided information about when results would be available, 31 discussed the manner in which the results were reported to physicians, and 36 indicated how parents might obtain these results. As the number of conditions included in screening continues to expand, there has been a move toward providing more general information about the types of conditions screened rather than detailed information about each condition.

**Prenatal Education**

Few programs actively support education programs about newborn screening during the prenatal period. Ten of 50 State programs reported that newborn screening brochures typically were distributed in obstetrical offices, and 14 of 50 indicated that there was routine distribution in birthing classes. No information was available concerning quality, readability or understanding of the brochure information. The growing number of conditions for which newborn screening can be expected, combined with the existing limitations (e.g., familiarity of child health professionals with the newborn screening system) to delivering education during the perinatal period, argues for a focus on enhanced education during the prenatal period. This area of need is currently being addressed by HRSA/MCHB through a contract with UCLA.

**Screening**

The timing of specimen collection and delivery to laboratories also varied. According to the NNSGRC 2000 National Newborn Screening Information Report, which included information from 28 programs at the time of this report, 74% of newborns were known to have been screened prior to 48 hours of age and 22% were screened after 48 hours. Twenty-two States reported that 2.7% of infants were screened prior to 12 hours of age, and 12.2% were screened between 12 to 24 hours of age. In several States as many as 30% to 40% of infants were screened between 12 and 24 hours of age. These timing issues may have direct implications for the predictive values of testing for some conditions.

Information about the timing of specimen delivery to laboratories was not readily available. The majority of programs rely on the United States Postal Service for specimen transport, with service varying from overnight delivery to up to a week in some areas. Most specimens arrive in the laboratories within 72 hours. However, in United States territories, such as Guam and States with relatively isolated and rural populations, delivery may take a week or more. It is suggested that specimens be transported by courier services that allow for receipt at the testing laboratories within 24 hours.

The timing of specimen collection and delivery is variably tracked. For diagnosed cases, programs generally record date of birth, date and time of specimen collection, date of receipt in the screening laboratory, date of laboratory report, and date of diagnosis. However, since establishing an etiologic diagnosis may be an iterative process that increasingly refines diagnosis, it can be difficult to define the time at which "diagnosis" is established. The date when initial diagnostic tests are ordered has been used as a substitute for date of diagnosis. Some programs monitor the date of initiation of treatment, but variations in the treatments for different conditions and the tendency to institute low-risk treatments in ambiguous, nonclassical cases renders this less useful unless viewed in the context of individual diagnoses. Most newborn screening programs presently operate on a 5-day work week. Some conditions can be life-threatening (e.g., MSUD, CAH, GALT, organic acidurias, fatty acid oxidation disorders, urea cycle disorders) within a few days after birth, so it is desirable to initiate specimen processing within 24 hours of specimen receipt in the laboratory, with a 5-day turnaround time between birth and the availability of the test results. However, it should be emphasized that detection of disease in the presymptomatic phase is one of the basic principles and values of screening.

The handling of screen-positive cases also was evaluated. Essentially, all newborn screening laboratories utilize a follow-up coordinator for reporting and tracking screen-positive results. For the most part, a positive result is reported only after the laboratory has verified the original finding through a second analysis of the original specimen. However, for some of the most time-sensitive conditions characterized by short-

term mortality and morbidity risks (e.g., CAH, galactosemia, isovaleric acidemia, MCAD, maple syrup disease, and some of the other metabolic diseases), preliminary positive results may be reported prior to repeat testing. These results are generally reported by telephone to the health professional identified by the newborn screening submittal form or by the birthing facility and/or the newborn screening consultant. The expert group recommends standardization of reporting procedures, including: the result, the reference range, the nature of the abnormality, and an indication of the speed and progression of clinical symptoms in the absence of intervention.

Screen-negative cases are often handled quite differently from the screen-positive cases. Some programs group normal results for batch reporting, waiting until all assays have been completed. Among the more significant potential problems identified in reporting of results is the risk of interpreting screening results as equivalent to diagnostic testing results. Screening results that are in the normal range may not have the same negative predictive value as is the case for diagnostic specimens obtained due to symptoms.[39] Additionally, it is increasingly apparent that age (developmental, chronological) and condition (acute affected, feeding status, transfusion status) of the newborn when the specimen was collected can affect the test results and their interpretation.[40]

Further, the use of general terms such as "amino acids normal" or "acylcarnitines normal" in reporting of screen-negative results is an issue. The general lack of knowledge among clinicians of newborn screening programs and the screened conditions makes these types of results not useful. On the other hand, clinicians may not want to take the time to read through long, detailed, normal reports. A report indicating all that was normal in an MS/MS screening profile could require considerable information to reflect the varying degree to which different conditions had been ruled out. At the same time, it can be argued that detailed reports are necessary. For example, if an infant moves from one State to another that has a different screening panel, the results may be misinterpreted if they refer to a general group of tests rather than being delineated by condition.

The fact that two categories of screening tests and result reporting are proposed also complicates this issue. States vary in which primary-target conditions they choose to detect and the technology they use to detect them. In addition, there is variability in the testing strategies (e.g., use of second tier testing) and the cutoffs the program chooses to define cases. Diagnosis and Follow-up continues to consider these reporting issues.

Most programs report screened-negative results to the location identified on the newborn screening collection card, which in many cases is the hospital of birth and not necessarily the infant's medical home. It has been observed in NNSGRC reviews of newborn screening programs that many hospitals do not routinely track the results and when the test results arrive at the hospitals, they are simply filed in the medical records without review. In addition, the tracking of newborn screening results to ensure that results are obtained on all screened newborns, while desirable, is not a uniform hospital practice. As screening expands for the pediatric population, the medical home should consider incorporating verification status of newborn screening results and keep such records easily accessible in a manner similar to those used for posting immunization status to medical records. Recent efforts by HRSA/MCHB to support the development of integrated and linked information systems that include newborn screening information for health care providers' direct access is an important development that may improve communication of screening results to the medical home and other appropriate health care facilities for the newborn. Additionally, national standards for the reporting of newborn screening results should be considered (similar to ACMG guidelines for prenatal DNA and other test report guidelines).

The use of second- or third-tier testing also was addressed in the work group's assessments. This practice is fairly common in newborn screening laboratories. Almost all States use a second-tier test for CH, either T4 or TSH depending on which was used in the initial screen. These second-tier tests are commonly done on the original bloodspot sample and are distinguished from repeat testing, which involves repeating the same test on the original specimen, or second tests that require a fresh sample. Some programs use a second-tier fluorometric test following an initial bacterial inhibition assay for PKU. DNA testing as a second-tier test to detect high-frequency mutations is done in some programs for CF, hemoglobinopathies, MCAD, LCHAD and galactosemia, and some are considering second-tier testing by MS/MS for CAH. With expanded newborn screening (including hearing loss screening) identifying as many as 1:250 newborns who will require diagnostic confirmation (B. Therrell, personal communication), the need to assess the capacity of the follow-up system is apparent.

Procedures for repeat testing in the newborn screening laboratory on the original bloodspot also were assessed. Essentially all newborn screening testing laboratories employ a QA step of retesting the original spot to confirm preliminary positive results. Some laboratories use a different method on second tests as a QA check. Retesting original bloodspots is distinguished from second-tier testing using a different test, and also from repeat screening, which uses a new specimen on which confirmatory testing is done. Routine repeat screening of all newborns is required in eight States, and several others strongly suggest second screening. There are specific circumstances (e.g., unsatisfactory specimens, acutely ill newborns in the NICU) under which repeat screening is commonly required. Because of the possibility of biologic false-positives, 29 States recommend/require a second specimen if tested prior to 24 hours of age and seven States require a second specimen if the newborn is tested before 48 hours of age. False-positives for CH and CAH are common in premature infants but can be dealt with through retesting when the infants are a few days older and their endocrine systems are more mature. Improved testing specificity on the initial specimen also can be achieved by using a nomogram more specific to the gestational age of the infant. False-negatives are the greater concern, since they may

not be recognized easily. Programs that mandate a second test for CH report finding 5% to 15% of their total caseload through the second test, but these cases have not been studied. This number is reduced by about 50% when TSH is used as the initial screening analyte. Over half of the cases of the classical simple virilizing form of CAH may go undetected on an initial screen due to biological factors.

**Reporting and Follow-up**

Follow-up is the term commonly used to describe the process of reporting abnormal screening results to the medical home, specialist, and/or guardians/parents and the initiation and tracking of the next steps in evaluation. Follow-up can be divided into two categories, short- and long-term follow-up. Short-term follow-up includes those activities that ensure all infants are screened, abnormal results are appropriately and expediently handled, and affected infants are promptly identified, appropriately referred, and treatment initiated where applicable. Long-term follow-up extends the period of follow-up substantially to monitor continuously the medical management and care coordination of those affected who require such services. Long-term follow-up also allows assessment of efficacy, sustainability, and safety of early treatment intervention, and can uncover new disease/treatment outcomes, and is valuable for demonstrating utility or limitations of screening.

Newborn dried bloodspot screening follow-up generally has functioned independently of newborn hearing screening follow-up, although many aspects of the follow-up procedures are similar and sometimes duplicative in terms of effort. Programs should minimize the number of places to which health care professionals must go to get information about their patients. Advances in information technology would allow direct and immediate access to screening test results, benefiting infants, health care professionals and screening programs. The experience of the newborn dried bloodspot programs could inform the hearing screening programs that have significant loss to follow-up of patients.

There is also some variation in how programs follow-up unsatisfactory specimens. Some State laws and program regulations place the responsibility for a satisfactory specimen on the specimen submitter. In such cases, the program tends not to pursue unsatisfactory specimens, electing to let the submitter perform its responsibility to the program. It is not clear that such practices had any impact on the liability issues that seem to have been the reason for such program practices to have arisen. In other cases, programs exercise their follow-up responsibilities in much the same way as they handle screen-positive cases. CLIA regulations require that a testing laboratory show that it has a procedure for improving specimen submissions in instances where there is unsatisfactory performance on the part of the specimen submitter.

Inadequate demographic information (e.g., patient's name, weight or age at the time of collection) also may render a specimen unsatisfactory. Most programs lack a strict enforcement policy regarding specimen rejection related to their rules governing certain demographic information. Often the initial responsibility for determining the acceptability of the specimen's demographic information falls to the clerical personnel performing the check-in process.

In order to improve the overall quality of specimens provided to newborn screening laboratories, the best approach is to minimize the number of unsatisfactory specimens and to ensure that an appropriate submitter education program is in place. It is best to have a designated person responsible for monitoring the quality of infant demographic information and for ensuring that accurate and complete information is part of a total quality management approach to laboratory operations. Compliance with requests for specimen demographic information must be monitored and action must be taken regarding noncompliance.

Most large States use computerized follow-up systems. Because these systems can be adapted to automated error surveillance, programs are encouraged to pursue routine quality checks using their computer systems. In the few States with computer generated submitter profiles, the profiles are used to improve the quality of specimens and information submission by, for example, monitoring periodic error rate reports. Those using computerized reporting and tracking systems have reported improvements on the part of submitters when profiling reports are used and submitters receive feedback from the reports.

In the event of a screen-positive result, most programs rely on information submitted with the newborn screening specimen to identify the newborn's physician or medical home. However, many newborns lack an identified child health professional at the time of release from the hospital. Often, the demographic information submitted with the specimen lists the nursery physician or on-call physician as the physician of record. Although identifying the appropriate child health professional may be a challenge, most newborn screening programs attempt to meet this challenge. Contact with the subspecialists is usually easier, since the group is smaller and is usually more intimately involved with the newborn screening program. In the interest of further closing the gaps in the system, it would be useful if hospitals were able to ensure that a follow-up appointment has been made for all newborns prior to their hospital discharge. At a minimum, the hospital nursery staff should work with families to identify the infants' medical homes and ensure that contact information for all infants is up to date.

Once the screen-positive case has been referred into the health care system, most programs have follow-up protocols that include tracking the patient until treatment has been initiated. Some programs subcontract this responsibility to regional medical centers and do not actively pursue this information, having transferred the responsibility for this in their contracts. However, this practice may complicate ready access to short- and long-term information that would be useful for program evaluation. Some States are developing systems that allow information integration and program linkage to improve tracking of screening results and patient outcomes. For example, some use bar codes that link newborn screening filter paper cards with birth certificates, and others have considered

including the newborn screening information on the face page of the medical record where vaccination information is placed to facilitate monitoring. In any case, a plan should be in place for exhaustive and documented confirmation of follow-up. Follow-up coordinators should link repeat specimens to initial specimen records, and all programs should obtain short- and long-term follow-up information.

A variety of methods of screen-positive results notification have evolved within newborn screening. In most programs, once the follow-up coordinator has provided results to the child health professional, the child health professional or a member of his or her staff informs the family of the screening results. Some programs notify both the child health professional and the family. Education is an important aspect of the notification of parents and health care professionals. Some States have developed culturally and linguistically appropriate educational materials for families but there is limited availability of similar materials for child health professionals and specialists.

Once the family is informed of the test results, the child health professional determines the need for and extent of subspecialty involvement, unless the program's follow-up is conducted directly through subspecialists. Not all conditions have similar demands for the timeliness or complexity of follow-up. The availability of informational materials for child health professionals that would facilitate their ability to participate actively in a collaborative management approach to their patients' care would be useful. Such information could include immediate management issues and relevant subspecialist referral sites. The work group on Diagnosis and Follow-up developed templates for such informational materials that have been pilot tested at limited sites. They are the basis of ongoing work developing templates for all conditions in the core panels, as well as those in the secondary target category. (Examples of these templates can be found in Appendix 3.) Although guidelines for immediate management could be readily developed, there is little standardization of parameters by which one would qualify an experienced subspecialty provider. Further, some parts of the country may have limited availability of experienced pediatric and subspecialty care health care professionals. This is particularly apparent in the area of inborn errors of metabolism; there are currently 53% fewer board certified biochemical geneticists in the United States than were practicing in 1990 and a limited number of trainees. In such circumstances, an organized system to link child health professionals with specialty care professionals would be useful. This could be accomplished through the developing HRSA/MCHB Genetics and Newborn Screening Regional Collaboratives that are intended to make national and regional services and resources accessible at the local community level.

Once confirmation of diagnosis is available to the child health professional or subspecialist, it is common for this information to be communicated promptly to the State newborn screening program. It is important that all programs obtain confirmatory outcome reports in order to fulfill their public health mandate.

**Diagnosis**

There is a complex relationship between the definition of screen-positive test results and the definition of the genetic condition itself. Upon identifying a screen-positive infant, algorithms through which diagnostic confirmation is obtained are followed. Some steps may involve the screening laboratory as is the case with second-tier tests while others involve the clinical and laboratory evaluations that lead to the final diagnosis. It is only after significant testing in a general population that the full breadth of the phenotype of the genetic condition in question is well understood. Hence, it becomes important to maintain communication between the health care professionals and the screening programs related to the false-positive and true-positive results. It will also be important to reconsider what constitutes a false positive result since a particular screening result may be associated with either a core condition panel or a secondary target condition. Further, it is important to develop mechanisms through which programs can be made aware of patients identified outside of the program in order to adjust program parameters to avoid "missed" cases. Finally, given that genetic tests can provide information about affected individuals and carriers, clear policies should be in place about communicating such information.

**Management**

Many programs do not have educational materials to facilitate and optimize patient care once a patient is diagnosed. Such information is commonly in the purview of the experts who develop guidelines for treatment. Information dissemination practices that facilitate collaborative management between the child health professionals and specialists would be useful.

Over the longer term of intervention and treatment there is usually insufficient information shared between health care professionals and the programs, and contact beyond the initial treatment phase is rare. This gap might only be filled through the development of information collection systems that facilitate the integration of program information with other health care information.

The availability of and access to therapeutic interventions varies among the States. Some States provide funding for medical foods†[1] either completely or on a sliding scale based on income. Costs not covered by insurance may be covered through Title V funds and Medicaid. However, they are less likely to fund genetic counseling, penicillin for sickle cell disease, or thyroid hormone replacement therapy.

A definition of the range of health care professionals considered necessary for managing a particular condition is limited. Medical and nonmedical services are generally defined by the health care professionals to whom the infants have been referred. However, because almost all programs provide no funding for health outcome evaluation, few long-term studies exist. Beyond one to three years of age, there is little coordinated or systematic monitoring by the programs.

**Program Management**

Programs use a mix of models for management and development of their newborn screening activities. Many States have external advisory committees, although some rely only on internal advisory groups, which may not include consumers and experts for conditions considered by the programs.

### B. Program evaluation

Several of the goals of this project are aimed at standardizing language and identifying the data or information needed to evaluate newborn screening program performance. Historically, newborn screening programs have been evaluated only internally, with the exception of the screening laboratory, which generally must meet CLIA requirements even though some of the analytes may not be specifically covered. Since 1987, HRSA/MCHB has made available to the States consultative program reviews by a team composed of experts in various aspects of newborn screening activities, and this has been continued as a responsibility of the NNSGRC. Besides providing annual State data specific to the Title V Block Grant performance measure, programs voluntarily report their program performance data to the NNSGRC for compilation and publication as an annual newborn screening data report. These reports are available at the NNSGRC website and can be used for inter- and intraprogram comparison (See www.genes-r-us.uthscsa.edu). Uniform performance measures, however, could enable better and more standardized comparative assessment of newborn screening programs. Performance standards should be related to the needs of those with the specific conditions identified. Uniformity of language and standardization of performance measures will allow programs to move from independent evaluation to a comparative system targeted at high quality and efficiency.

**Program Standards**

A fundamental goal of newborn screening is benefit to the newborn by identifying a treatable condition. Variability exists among the conditions in the core panel regarding the speed with which they must be treated in order to minimize or eliminate the negative consequences of the condition. In newborn screening programs, speed of screening and reporting results is sometimes driven by the conditions that have the most demanding time needs. For example, an elevated 17-hydroxyprogesterone indicates a high likelihood that classical CAH is present and should therefore be pursued promptly, since in some instances death can occur from salt wasting within the first two weeks of life. Similarly, an elevated C8 acylcarnitine indicates a high likelihood that MCAD is present and should therefore be pursued promptly, since in some instances death can occur within the first two weeks of life. This contrasts with the finding of hearing loss, for which the interventions can be delayed for two to three months without significantly affecting speech development. The importance of education of families and the medical home about timing and the consequences of later notifications is apparent.

Appendix 4 lists specific steps in the newborn screening program process that should be monitored. Program performance can be improved by integrating data monitoring into policies and procedures and then modifying programs as problems are identified. Furthermore, development of a uniform approach to data collection and program evaluation allows for the comparison of program performance among States.

**National Programs of QA**

On a national basis, there is no comprehensive QA program for newborn screening aside from that provided for screening laboratories by CDC (see Fig. 10 ). CDC offers a proficiency testing and quality assurance program specifically for newborn screening laboratories—the Newborn Screening Quality Assurance Program. The newborn screening laboratories are regulated under CLIA of 1988. FDA provides additional oversight of manufacturers who provide testing products to newborn screening laboratories, and CDC provides a service that validates the filter paper bloodspot collection devices. The NNSGRC, funded by HRSA/MCHB, provides consultative program reviews that include all aspects of the newborn screening system (upon the official invitation of individual State newborn screening programs), and collects and assimilates national newborn screening data.

The Joint Commission on Accreditation of Hospital Organizations (JCAHO) plays a role in the oversight of activities within hospitals. For several reasons, JCAHO's activities have not been specifically directed toward the hospital's role in newborn screening. Even though birth hospitals collect the vast majority of screening specimens, record demographic information, and receive newborn screening test results, hospitals have not traditionally been held accountable to JCAHO for newborn screening activities per se. Historically, hospital responsibilities for tracking newborn screening testing results have been varied, particularly since the newborns are usually not in the hospital when the screening results are completed and returned. Most State screening regulations are silent on hospitals' responsibilities, though some include specific requirements, and hospitals and administrators can in some States be held liable if newborn screening practices are improperly performed. Oversight of newborn screening has been complicated by the fact that the oversight of clinical activities is limited compared to the regulation of laboratories, which includes maintaining records of specimen submission and result reporting. In many hospitals, newborn screening specimens are collected and submitted to the screening laboratory directly from the newborn nursery, bypassing some areas of this laboratory oversight. Hospitals appear to assume greater responsibility for screening conducted within the nursery, for example, screening for hearing loss. In such circumstances, hospitals have a clear responsibility to make patients aware of any critical laboratory information stemming from their hospital stay. However, since hearing screening results are immediately available, the task of initiating notification and arranging for next steps in evaluation is simplified.

Discussions are ongoing regarding the possibilities of improving the ways in which hospitals provide information to newborn screening programs to ensure that adequate information is available in a timely manner for recontacting families or health care professionals and establishing follow-up while still maintaining appropriate privacy of the patient's medical information.[2] At the level of diagnosis and follow-up, there are several programs that have worked toward ensuring quality. Some organizations, such as CORN, AAP, ACMG, and the Society for Inherited Metabolic Disorders (SIMD), have been involved in the development of practice guidelines for the diagnosis, treatment, and management of many of these conditions. In addition, there are programs with "deemed" status through CLIA that offer proficiency testing and inspections of the laboratories providing diagnostic services for the conditions included in newborn screening programs. However, at the present time most analytes that are screened are not included in this program, although their addition is under active discussion.

Some programs have developed internal QA programs that variably address the components of the newborn screening system. While all States tabulate the number of tests done, many cannot relate tests to birthing records in order to ascertain the percentage of newborns screened. On the other hand, programs routinely track time from birth to diagnosis and treatment, and the numbers of newborns lost to follow-up, which are extremely important aspects of the screening system. Most programs maintain records of unsatisfactory specimens but they vary in follow-up actions and educational programs to improve specimen quality. In this respect there is perhaps a role for the federal government in providing some form of national program oversight. Furthermore, there are very different forms of oversight for laboratory services than for clinical services. In order to continue to improve the quality of newborn screening programs, several actions should be taken:

1. There should be uniformity in the types of data collected (see Appendix 4) by programs in order to compare program performance among States. In addition, reporting to a central authority should be required.
2. Periodic performance reviews of all components of newborn screening programs should be required. This should be a federal responsibility.
3. Language and terminology should be standardized in order to better compare performance among programs.
4. Turnaround time in reporting screen-negative results should be improved.
   a. At a minimum, all results from the initial screening test (some States perform a second test later) should be available less than five days after the blood sampling for the first posthospital discharge visit to be of use in this clinical visit and to facilitate awareness of lifelong screening. Most results should be available within two days of the specimen arriving in the laboratory, and specimens should arrive in the laboratories within three days of collection.
5. Diagnostic laboratory QA programs should be enhanced to include all conditions screened in newborns.
6. Organized systems to allow for the collection and analysis of data about patients are important in defining the standards to be met and improving our understanding of these typically very rare conditions. Data from population-based screening are the optimal source of unbiased information about conditions and required reporting should be instituted.
7. Hospitals and JCAHO have significant roles to play, and standards need to be developed to improve quality, minimize errors, and facilitate tracking of newborns requiring active participation in testing follow-up.
8. All newborn screening laboratories should be CLIA-certified and should participate in CDC and CAP/ACMG proficiency testing programs or other equivalent programs as applicable.
9. All States should have an active system-wide newborn screening QA and total quality management program.
10. To bring uniformity to programs across the country and thereby create a more equitable system for all Americans, national oversight and authority must be provided with adequate resources. Consideration should be given to institutionalizing the role of the HRSA-funded NNSGRC, which currently offers on-site expert consultative reviews to the State newborn screening programs.

### C. Cost-effectiveness analysis

This project focused primarily on a scientific analysis of conditions and the features that should be considered when deciding whether they should be included in a newborn screening program. However, costs often are the basis on which such decisions are made. Review of the few available cost-effectiveness studies of newborn screening suggests that often, they may be too limited in scope. Some studies have focused on the short-term costs and benefits of the screening stage and the immediate steps following the identification of a screen-positive infant. Most address tests for only a small number of disorders, and none has explored the cost savings and clinical benefits of tests such as MS/MS.[41–46]

A basic cost-effectiveness analysis was conducted to better inform our decisions. Costs and benefits related to screening for particular conditions or groups of conditions were evaluated after mapping them over major disease outcomes (e.g., life expectancy, cerebral palsy/stroke, seizures, developmental delay, hearing loss, vision loss). Costs were obtained from the literature.[2,42,43,47–51] Benefits were determined from expected outcomes with and without early treatment or intervention. Quality-adjusted-life years (QALYs) were then compared to costs. Where appropriate, tests capable of being multiplexed with other tests for different conditions were assessed independently and as a group. Results were found to be stable by sensitivity analysis.

The results of these analyses indicate that all newborn screening programs evaluated improved outcomes and most reduce overall costs (Carroll and Downs, in press). Screening

for CAH added increased cost per QALY gained, but the cost was well within the range conventionally considered cost effective. Screening for galactosemia was the only strategy that would be considered not cost effective in the base case analysis. However, under some reasonable assumptions, it can be shown to be cost effective. The identification of potentially affected individuals at such an early time in life leads to many years over which the benefits accrue and, in aggregate, the benefits outweigh the costs.

Technologies such as MS/MS further save money due to their multiplexing capability and low screening false-positive rates. MS/MS, used to screen for multiple conditions, had the greatest impact on outcomes and saved the greatest amount of money in the analysis. Virtually all screening for conditions that are treatable with significantly beneficial outcomes can be justified with benefits increasing as more conditions are included. The analysis also showed that clinical benefits and savings depend on low false positive rates and timely follow-up and treatment of positives, emphasizing the importance of an integrated screening and follow-up program.[41–45,52]

### D. Information gaps and a research agenda

#### Data and Analytical Needs

*Screening*

The evidence base for disorders potentially amenable to screening is limited and the questions that must be answered to inform our decisions about the future of our newborn screening programs are numerous and the issues complex. There are cutting edge new technologies emerging that can have a significant impact on screening programs. However, tech assessments have limited capacity to identify issues about promising technologies early in their development (e.g., is there sufficient capacity in the system to test the 4.1 million United States newborns? Are the tests adequately validated?). This raises important questions about how to implement new technologies for screening. Historically, as new technology is validated on a known cohort, it is then applied to a prospective screening cohort in a linked or unlinked (e.g., HIV screening) method, with or without reporting, and with or without randomization (e.g., CF). Many State newborn screening programs have awaited data from other State pilot or trial programs before investing in the costs of incorporating new technologies into testing and follow-up protocols. The potential for screening beyond the first few days of life is increasing. Determining how best to link existing public health activities (such as immunization) that occur at specific clinical points later in life offers opportunities to screen for additional conditions that are less amenable to screening in the first 24 to 48 hours of life. Information technology has opened up opportunities to improve the systems that support the medical home's integrated role in newborn screening and there is always the opportunity to improve informatics and communications and their integration into public health information systems and registries.

There is an ongoing and growing need to articulate a research agenda for the many conditions that are already part of newborn screening. For example, the impact on the optimal timing of screening of newborns in the neonatal intensive care unit that have received hyperalimentation or packed cell transfusions remains unclear.

*Follow-Up*

Many questions remain about the impact of screening for a larger number of rare disorders, as well as what the true significance is of a "false-positive" or "transiently abnormal" screening test.[53] These may require costly, long-term evaluation projects in order to obtain the statistical power needed to better understand these issues in rare diseases. Again, we may need a broader national approach to data collection and analysis.

*Diagnosis*

Considerable research potential exists in the area of diagnosis of these rare diseases. The preferred approaches and methods of diagnosis and confirmation of presumptive diagnoses remain to be determined and our understanding of the natural history of the conditions and the associated genotype-phenotype correlations can only improve. There are many questions to be answered for each of the conditions for which screening is currently offered. For instance, there is still little information available about the outcomes of infants identified in G6PD screening programs. The interrelated roles of genetic risk factors and the environmental exposures that trigger disease expression are areas where large collaborative research projects will be needed. The use of the National Children's Study as a component of newborn screening research offers a number of opportunities. Similarly, we need to understand the issues and barriers that lead to the lack of hearing screening follow-up to determine etiology.

*Management*

The emerging area of collaborative disease management offers many opportunities to improve our newborn screening programs. The nature of our health care system is such that the bridges between child health professionals and specialists must be strengthened. Issues of interest include: 1) how best to partner with the medical home; 2) how to facilitate the transition to adult care (childhood cancer survivorship model); and 3) what are the expected outcomes for the adults with these now chronic diseases. It is also likely that situations similar to that of maternal PKU will arise with other metabolic diseases, such as 3-MCC, or the endocrinopathies, such as CH. Long-term outcomes research will require organized systems of data collection and monitoring. There are also gaps in our understanding of treatment issues for many conditions (e.g., nonclassical CAH). We also need to elucidate the long-term behavioral and educational issues associated with children with conditions detected by newborn screening.

*Evaluation*

Program evaluation can also benefit from organized collaborative research programs. The creation of registries for long-term outcomes research and for system validation offers a clear pathway to improvement of the programs.

*Health Systems And Outcomes Research*

Our health care system continues to evolve in parallel with the evolution of the newborn screening programs. The increas-

ing diversity of the United States population necessitates that health disparities research as relates to diagnosis, management, and long-term follow-up of patients identified in newborn screening be enhanced.

*Education*

The trend toward more direct consumer involvement in health care decisions and prevention indicates the need for enhanced educational programs for the public. Further, the rarity and complexity of the many conditions already screened suggests a need for improved educational programs for the professionals. Opportunities remain to improve our understanding of the primary communication and education needs related to a screen-positive result in newborn screening. Similarly, many questions remain about the issue of appropriate decision-making relative to newborn screening. There is a need to understand the issues that arise in the delivery of prenatal education and determine the best models for such education while still working to broaden overall genetics public education. There is also a need to improve our understanding of how attention to cultural diversity and literacy could contribute to effective newborn screening programs. In order to better understand the limitations of and impediments to education, best practices models related to who provides services (e.g., birth educators, obstetrician gynecologists, subspecialists) need to be identified and there is need to understand how they can be provided outside the delivery room or nursery, and when they are best provided. The role for cross-specialty education and continuing medical education for health care professionals is also an area that would benefit from study. Last, there is considerable opportunity for research into the ethical, legal, and social issues that arise with expanded newborn screening and newborn screening in general.

*Health Systems As Related To Newborn Screening*

A better understanding of the organization and functioning of our newborn screening related health care systems would also benefit the continued development of programs. In particular, studies of systems of care that would offer the highest quality delivery of newborn screening services would improve the programs.

*Other*

There are numerous ancillary issues that relate to improving newborn screening outcomes. These include: 1) expanding screening opportunities prenatally and after birth when timing of testing, identification, and intervention offer additional value for health outcomes in the pediatric population; 2) ongoing research efforts to identify better and new screening and intervention strategies for rare and common disorders; and 3) continued research into outcomes of transiently abnormal screens to determine if such test results have predictive value for later diseases as well as to measure the psychosocial impact of such results (e.g., costs of vulnerable child issues). Some of the diseases for which postnatal newborn screening is recommended may be additionally benefited by prenatal detection; however, prenatal screening is not presently universally available. We may gain a better understanding of the incidence and spectrum of diseases associated with perinatal and early childhood mortality by implementing uniform child autopsy policies and procedures which ensure availability of appropriate studies (including metabolic and genetic studies for all perinatal deaths, including stillbirths) and early unexpected childhood deaths.

### E. Future needs

Hopefully all screening programs can benefit from a more robust national role and increased national standards and policies for newborn screening. Because so many of the conditions screened in newborns, or under consideration for screening, are rare, most States that undertake evaluations of the scientific basis for screening of conditions must rely on the same relatively small group of patients identified throughout the world. There is a potential national role in providing scientific evaluation of conditions and defining core condition panels. This would allow the States to apply the best science to their own considerations when determining their role in expanded screening. Practice guidelines also could be developed at a national level by interested organizations. There is also a potential expanded national role in oversight and enforcement, data collection, program evaluation, and the development of educational materials to support newborn screening.

Depending on the overall incidence of particular conditions, regional cooperatives should coordinate access to health care professionals, serve as coordinators and repositories for data collection, provide long-term follow-up capability when resources and expertise are limited, facilitate transition (and access) from pediatric to adult care, and provide education. The distribution of primary, secondary, and tertiary services is largely based on the incidence of a condition and the complexity of its short- and long-term diagnosis and management. For more common conditions with easier diagnosis and follow-up, there is likely to be sufficient local health care expertise for patient care. As incidence decreases and complexity increases—particularly for rare metabolic diseases—services become more difficult to access. Developing resources and infrastructure to ensure that health care professionals with appropriate expertise are available locally, regionally, and nationally will be important to ensuring access to high-quality services.

States also must retain their significant roles and responsibilities. They have a clear authority with regard to oversight and evaluation, as well as enforcement. There is a need to integrate the various systems of health care coverage and payment through flexible and comprehensive financing of services. Service coordination at both State and local levels must be considered, as well as program integration with the State Children's Health Insurance Plan, early intervention programs, Title V programs, Medicaid, and similar services.

In considering the national role in newborn screening, it is apparent that there are already significant barriers to the creation of a model newborn screening system in the United States. For example:

1. Financing across State and county lines is constrained by Medicaid rules;

2. Service delivery is fragmented on a disease basis;
3. There is lack of universal access and ability to access the medical home;
4. There is insufficient support to bridge geographic barriers;
5. It is difficult to identify experienced health care professionals for complex care (e.g., centers of excellence for genital reconstructive surgery for CAH; confirmation of metabolic diagnoses);
6. Misinterpretation of privacy regulations (e.g., HIPAA) (see Appendix 5 for discussion and clarification of HIPAA related issues in the context of a public health program);
7. There is underutilization and lack of uniformity of information technology;
8. Collaborative management and care is constrained by systems of reimbursement;
9. There is variability in State mandates;
10. State sovereignty sometimes dictates individual approaches; and
11. There is variability in financing of screening programs.

### F. Summary

In order for expanded newborn screening to be implemented universally, a well operating and standardized newborn screening system must be in place. At the present time there is significant variability among the State programs with regard to policies and practices employed after screening and in initial notification of health care professionals. The expert group evaluated the components of the system and their associated functions with a primary focus on the parts of the system that interface specialty care professionals with either the newborn screening program or the child health professionals.

A basic cost effectiveness study of newborn screening was conducted. The results of this analysis demonstrated that newborn screening is cost effective when compared to other recommended medical expenditures. This supports the recommendations made in Section One of this report regarding the need to expand the breadth of conditions that should be included in core screening panels and the secondary target category.

The scientific analyses and systems evaluations also identified gaps in our knowledge base and pointed to areas in which research is needed. The expert group recommends that:

- Programs continue to improve the components of the system beyond the initial screening, communication of those results, and ensuring that the newborn enters into short-term follow-up. To accomplish this:
- reporting procedures should be standardized
- reports of confirmatory results should be obtained
- There should be improved oversight (e.g., JCAHO) of the hospital-based screening activities to improve tracking of screen-positive cases;
- There should be more uniformity in the language and definition of the performance standards (e.g., repeat test, second test) monitored and reported by programs;
- The QA programs involving the diagnostic and follow-up system should be enhanced;
- National oversight and authority with appropriate resources should be provided; and
- Systems should be in place for collection of data about individuals identified as screen-positive in newborn screening programs.

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| Respondents | R-75 | R-76 | R-77 | R-78 | R-79 | R-80 | R-81 | R-82 | R-83 | R-84 | R-85 | R-86 | R-87 | R-88 | R-89 | R-90 | Mean | Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Incidence | 75 | 100 | 75 | 75 | 75 | 75 | 0 | 75 | 100 | 75 | 25 | 75 | 75 | 100 | 75 | 75 | 78 | 75 |
| Phenotype at birth | 75 | 100 | 75 | 100 | 100 | 75 | 100 | 100 | 100 | 100 | 75 | 100 | 100 | 100 | 100 | 75 | 91 | 100 |
| Burden if untreated | 100 | 75 | 100 | 75 | 50 | 100 | 75 | 100 | 100 | 75 | 100 | 75 | 75 | 100 | 100 | 75 | 78 | 75 |
| Method (S&S) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 91 | 100 |
| BS or Physical | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 84 | 75 |
| Throughput | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 200 | 200 |
| Cost | 50 | 50 | 50 | 50 | 50 | 0 | 50 | 50 | 0 | 50 | 0 | 50 | 50 | 50 | 50 | 0 | 99 | 100 |
| Multiple markers | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 46 | 50 |
| Secondary targets | 0 | | 50 | 50 | 0 | 50 | 50 | 50 | 50 | 0 | 50 | 50 | 50 | 50 | 50 | 50 | 31 | 50 |
| Multiplex platform | 200 | 200 | 200 | 200 | 0 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 0 | 46 | 50 |
| Treatment availability | 50 | 50 | 100 | 100 | 100 | 100 | 50 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 37 | 50 |
| Efficacy | 200 | 50 | 200 | 200 | 200 | 200 | 50 | 200 | 100 | 200 | 200 | 100 | 200 | 200 | 200 | 100 | 156 | 200 |
| Early intervention (IND) | 100 | 100 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 100 | 94 | 100 |
| Early intervention (F&S) | 100 | 50 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 50 | 159 | 200 |
| Mortality prevention | 100 | 0 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 180 | 200 |
| Diagnostic confirmation | 50 | 50 | 100 | 100 | 50 | 100 | 0 | 100 | 50 | 100 | 50 | 100 | 50 | 100 | 100 | 100 | 94 | 100 |
| Clinical management | 50 | 0 | 100 | 100 | 100 | 100 | 50 | 100 | 100 | 100 | 100 | 100 | 50 | 100 | 100 | 100 | 99 | 100 |
| Simplicity of therapy | 50 | 50 | 200 | 200 | 200 | 200 | 50 | 200 | 100 | 100 | 50 | 200 | 200 | 200 | 100 | 200 | 71 | 100 |
| | | | | | | | | | | | | | | | | | Sum of Mean scores | Sum of Median scores |
| Total score (individual) | 1600 | 1275 | 2050 | 2050 | 1725 | 2000 | 1475 | 2075 | 1800 | 1900 | 1750 | 1950 | 1950 | 2100 | 1975 | 1525 | 1799 | 2050 |

**Fig. 1.** Raw data for MCAD deficiency (16 of 90 total respondents)

| Respondents | R-105 | R-106 | R-107 | R-108 | R-109 | R-110 | R-111 | R-112 | R-113 | R-114 | R-115 | R-116 | R-117 | R-118 | R-119 | R-120 | Mean | Median |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Incidence | 75 | 75 | 75 | 50 | 75 | 100 | 75 | 75 | 100 | 75 | 75 | 100 | 75 | 75 | 100 | 100 | 78 | 75 |
| Phenotype at birth | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 100 | 100 | 91 | 100 |
| Burden if untreated | 100 | 100 | 100 | 75 | 75 | 100 | 100 | 100 | 75 | 100 | 100 | 100 | 100 | 100 | 75 | 100 | 78 | 75 |
| Method (S&S) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 91 | 100 |
| BS or Physical | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 84 | 75 |
| Throughput | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |  | 50 | 50 | 50 | 50 | 0 | 50 | 50 | 200 | 200 |
| Cost | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |  | 50 | 50 | 0 | 50 | 0 | 50 | 50 | 99 | 100 |
| Multiple markers |  | 50 | 0 | 50 | 50 | 0 | 50 | 50 |  | 50 | 50 | 50 | 50 | 0 | 0 | 50 | 46 | 50 |
| Secondary targets |  | 50 | 0 |  | 50 | 50 | 0 | 50 |  | 50 | 50 | 50 | 50 | 0 | 0 | 50 | 31 | 50 |
| Multiplex platform |  | 200 | 0 | 200 | 200 | 200 | 200 | 200 |  | 200 | 200 | 200 | 200 | 0 | 0 | 200 | 46 | 50 |
| Treatment availability | 100 | 50 | 100 | 50 | 50 | 100 | 100 | 0 | 50 | 0 | 50 | 100 | 100 | 0 | 100 | 100 | 37 | 50 |
| Efficacy | 200 | 200 | 200 | 100 | 100 | 100 | 100 | 100 | 200 | 100 | 200 | 200 | 100 | 100 | 100 | 200 | 156 | 200 |
| Early intervention (IND) | 200 | 200 | 200 | 200 | 0 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 94 | 100 |
| Early intervention (F&S) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 159 | 200 |
| Mortality prevention | 100 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 100 | 0 | 100 | 0 | 100 | 180 | 200 |
| Diagnostic confirmation | 100 | 100 | 50 | 100 | 100 | 100 | 100 | 50 | 100 | 50 | 50 | 100 | 100 | 50 | 100 | 100 | 94 | 100 |
| Clinical management | 100 | 100 | 100 | 50 | 50 | 50 | 100 | 50 | 100 | 50 | 50 | 100 | 50 | 0 | 100 | 100 | 99 | 100 |
| Simplicity of therapy | 200 | 50 | 100 | 50 | 100 | 100 | 100 | 0 | 50 | 0 | 100 | 200 | 100 | 0 | 100 | 200 | 71 | 100 |
| Total score (individual) | 1775 | 1775 | 1525 | 1525 | 1450 | 1700 | 1725 | 1475 | 1375 | 1475 | 1725 | 2050 | 1725 | 1100 | 1475 | 2100 | Sum of Mean scores 1663 | Sum of Median scores 1775 |

**Fig. 2.** Raw data for PKU (16 of 120 total respondents)

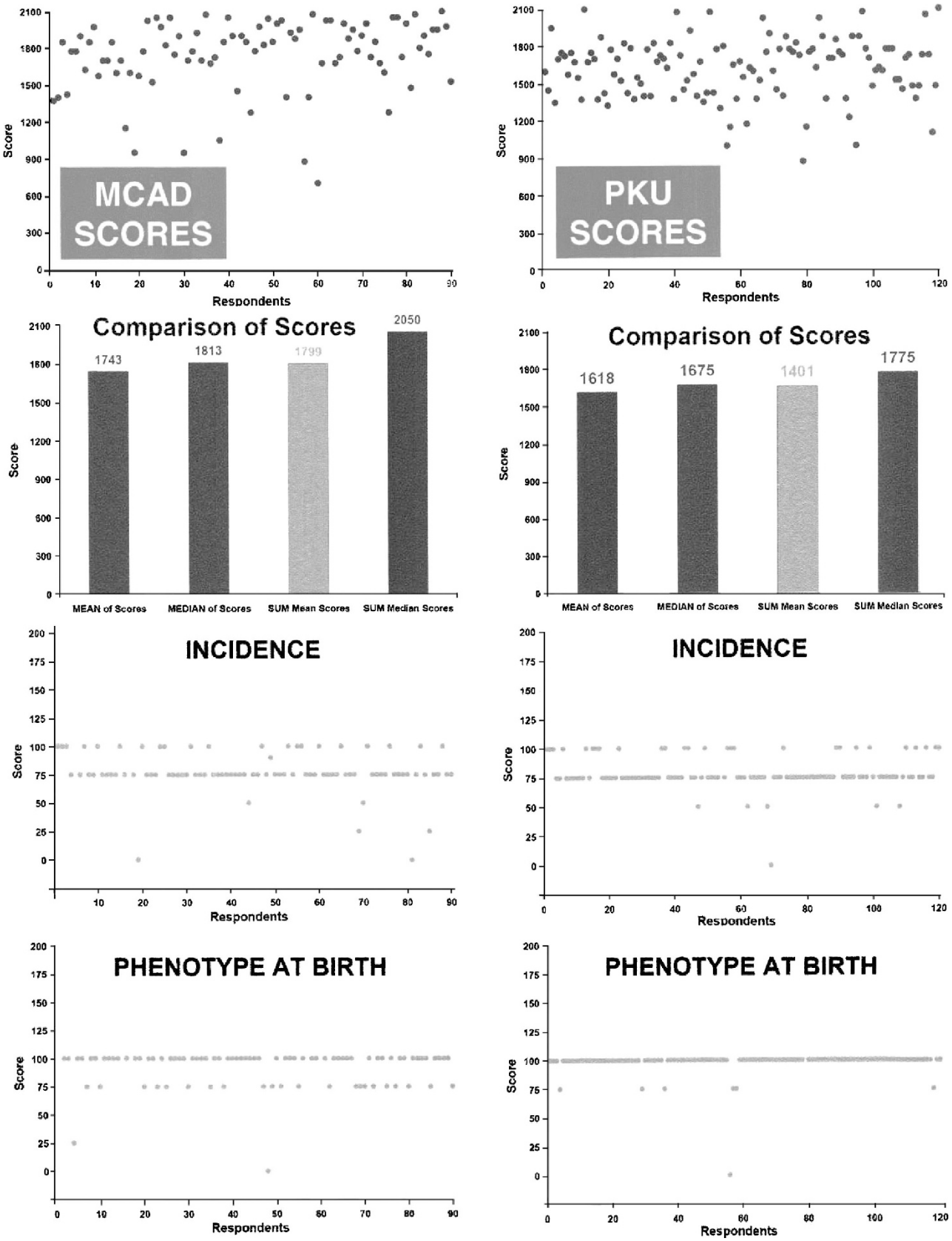



**Fig. 3a** Side-by-side comparison of MCAD and PKU for each of the criteria used

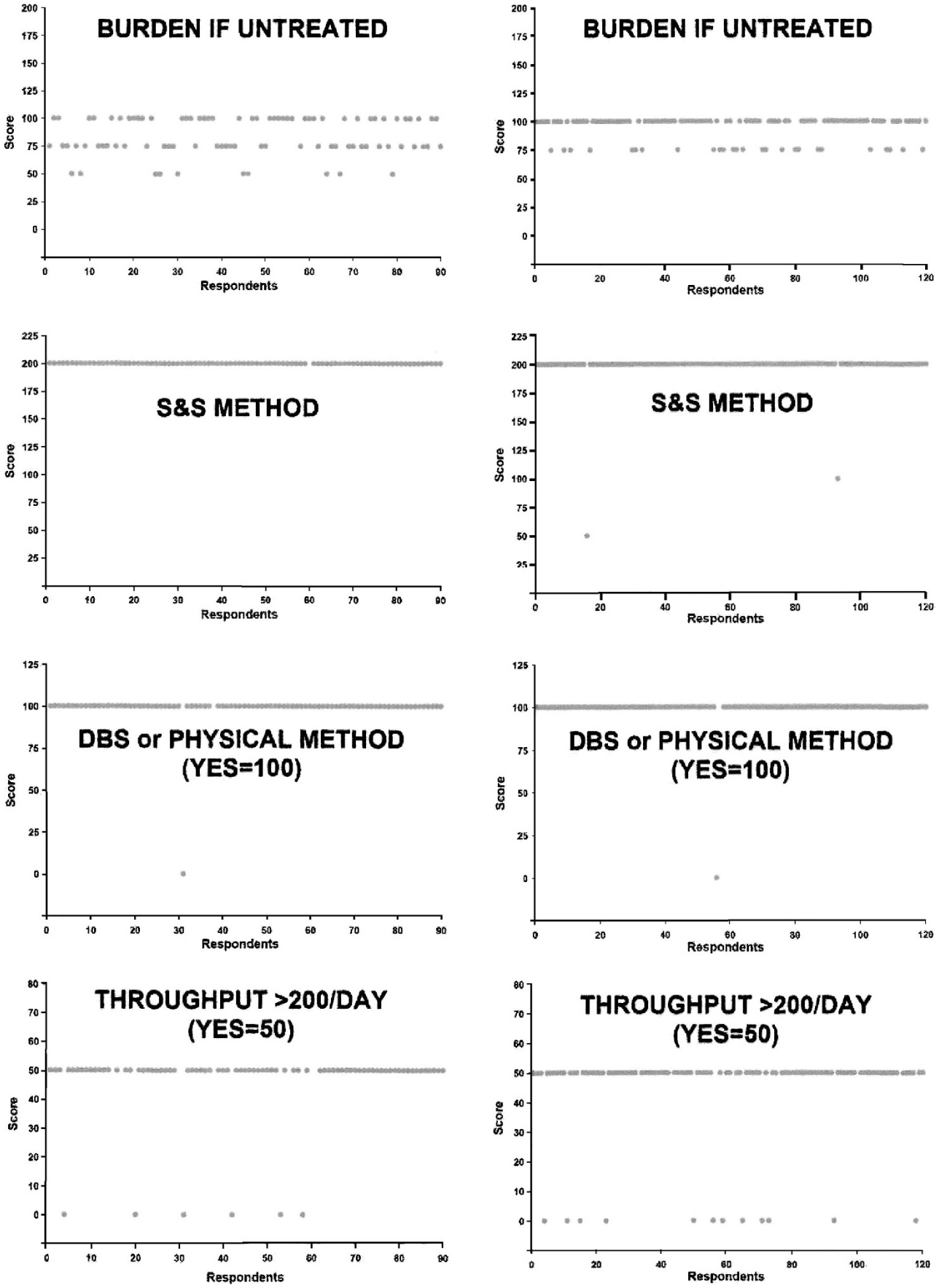



**Fig. 3b.** Side-by-side comparison of MCAD and PKU for each of the criteria used

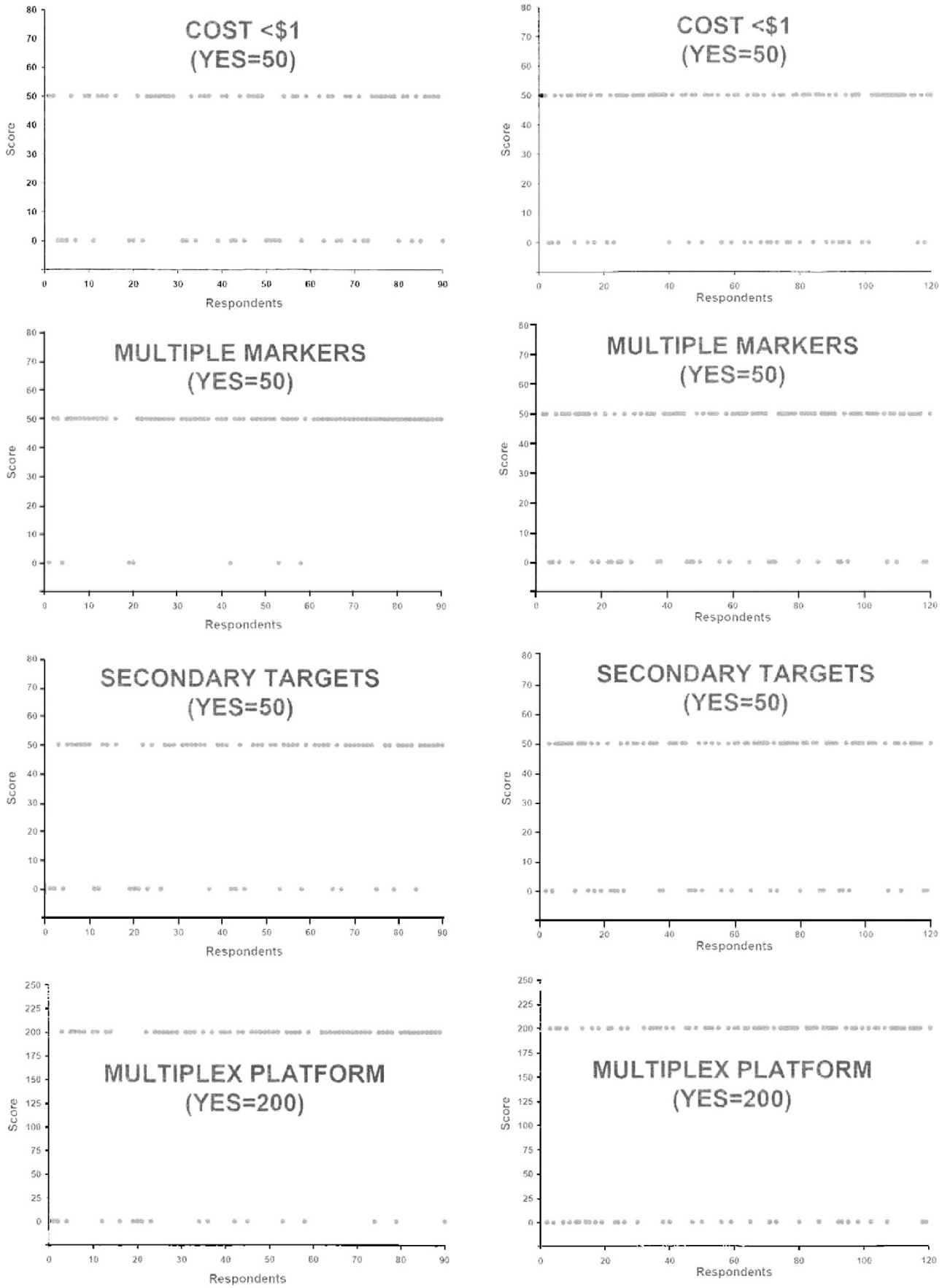



**Fig. 3c.** Side-by-side comparison of MCAD and PKU for each of the criteria used

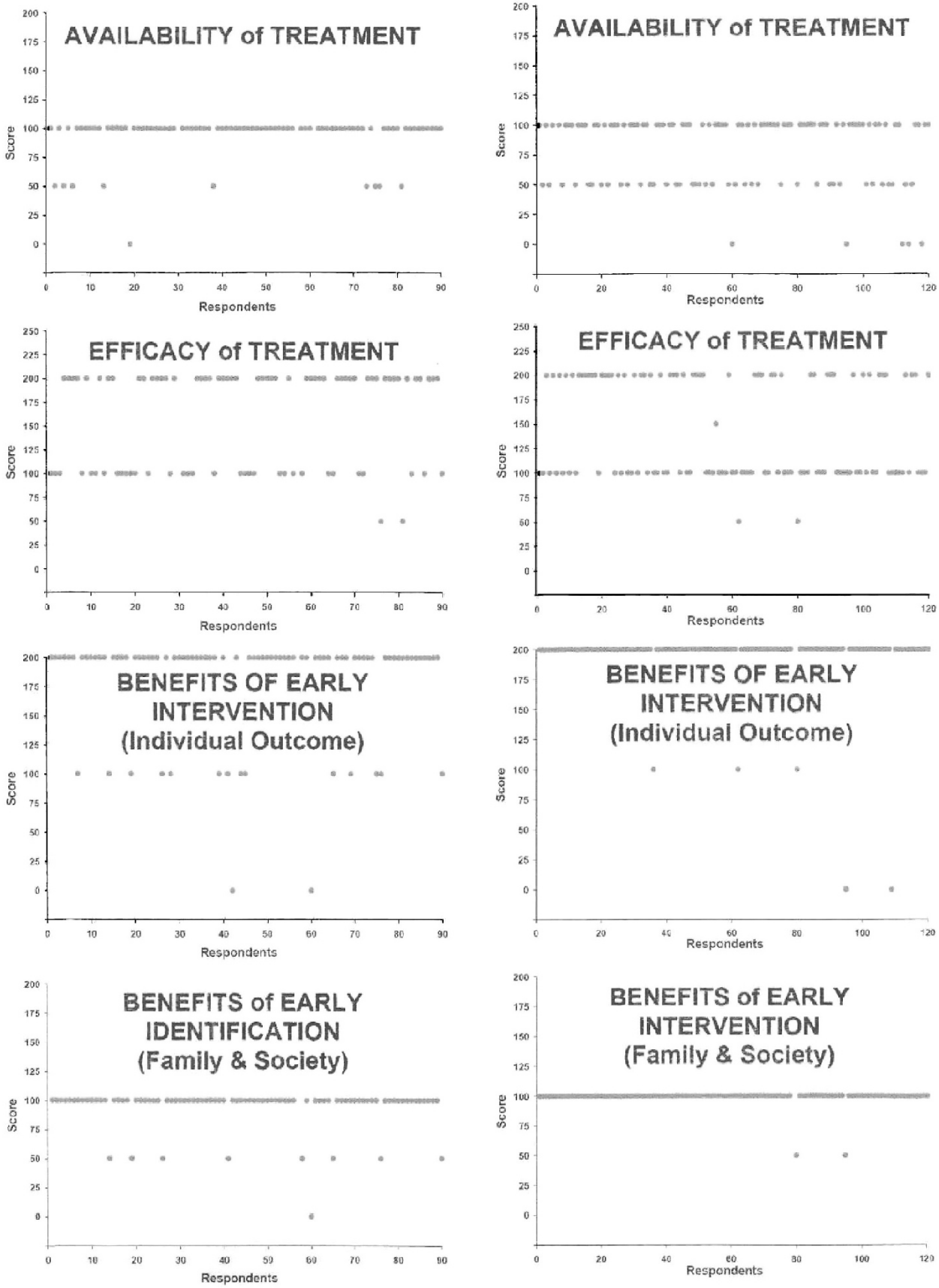



**Fig. 3d.** Side-by-side comparison of MCAD and PKU for each of the criteria used

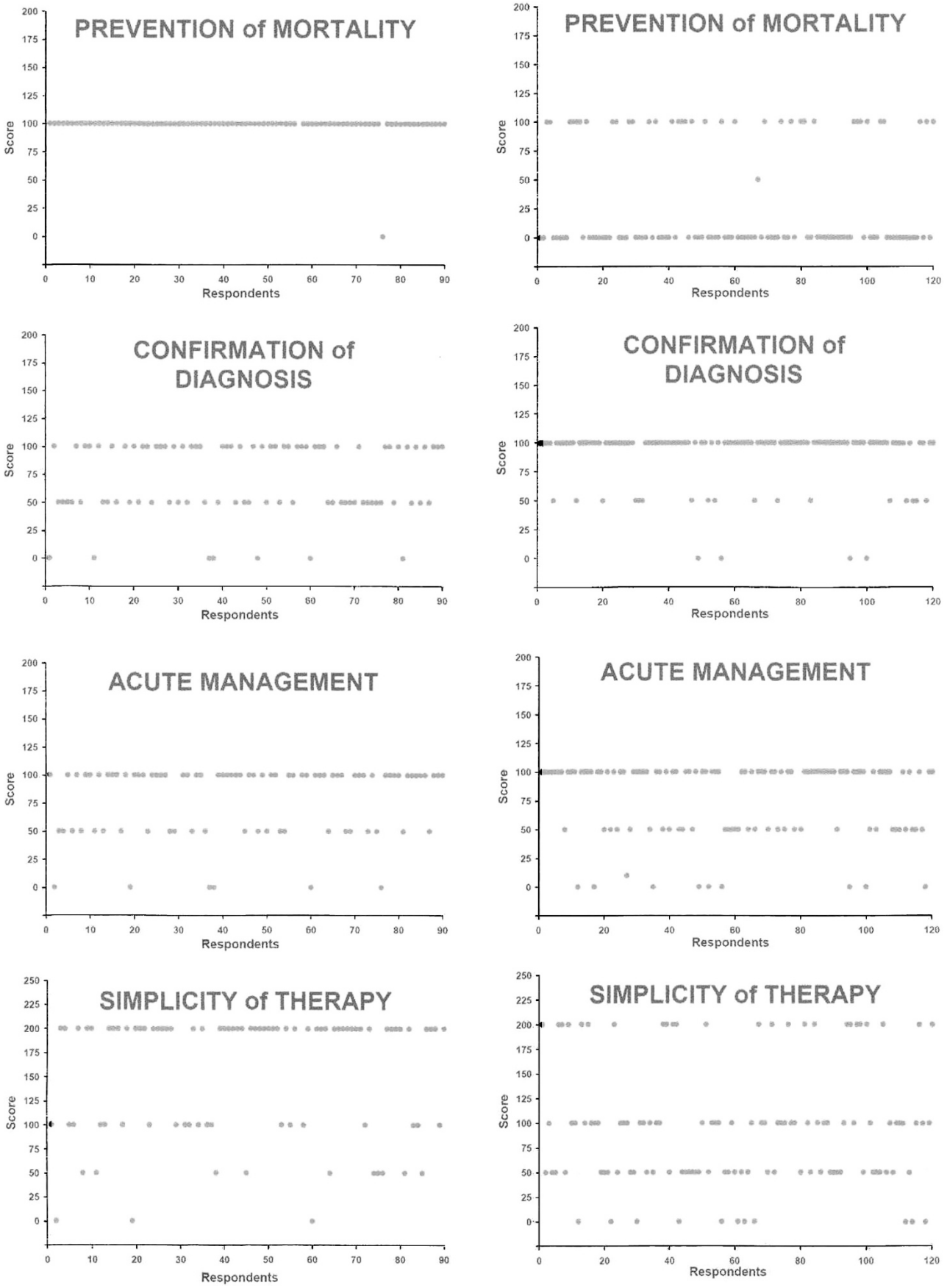



**Fig. 3e.** Side-by-side comparison of MCAD and PKU for each of the criteria used

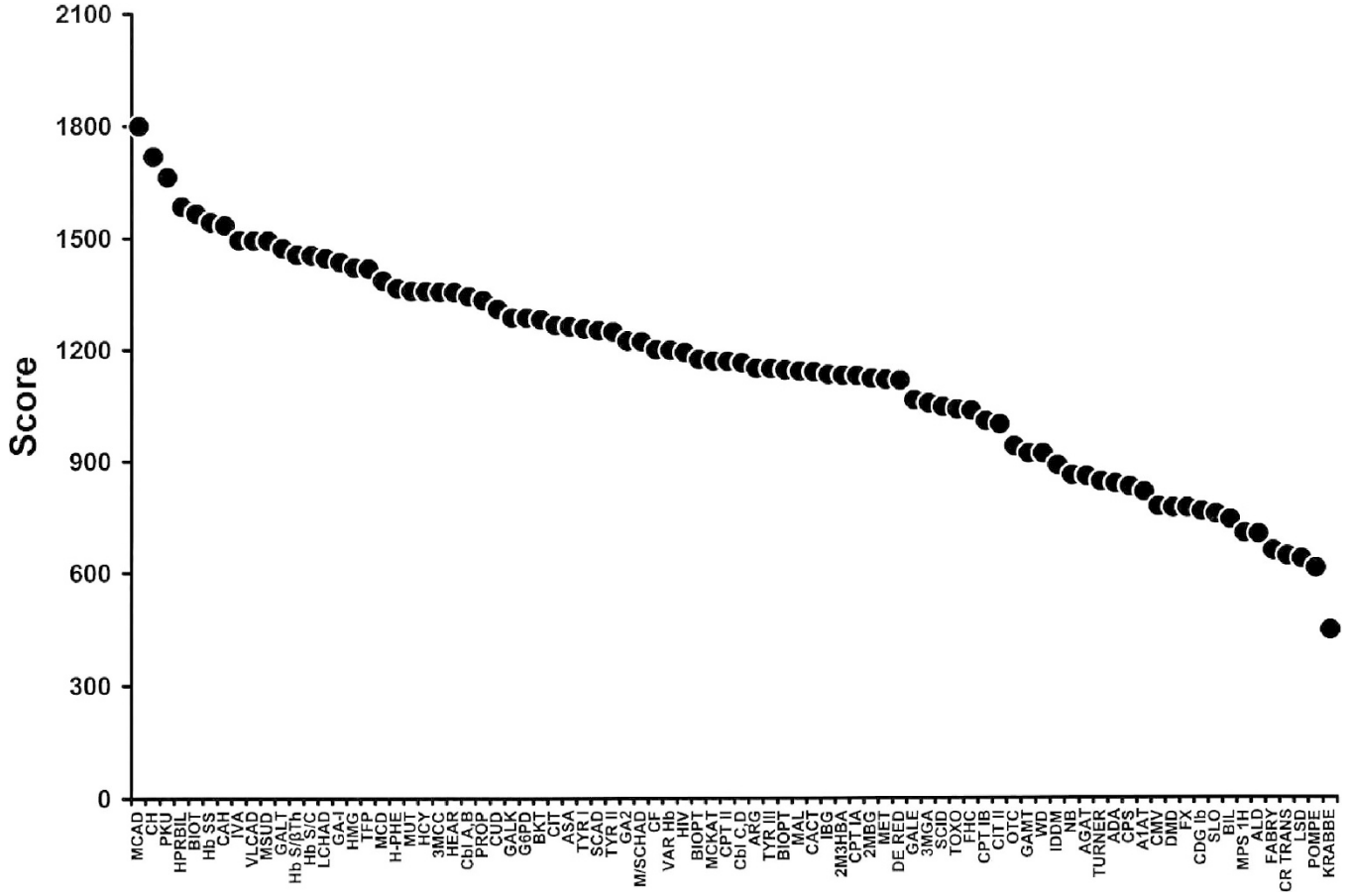



**Fig. 4.** Final scores (sum of mean scores) for all conditions

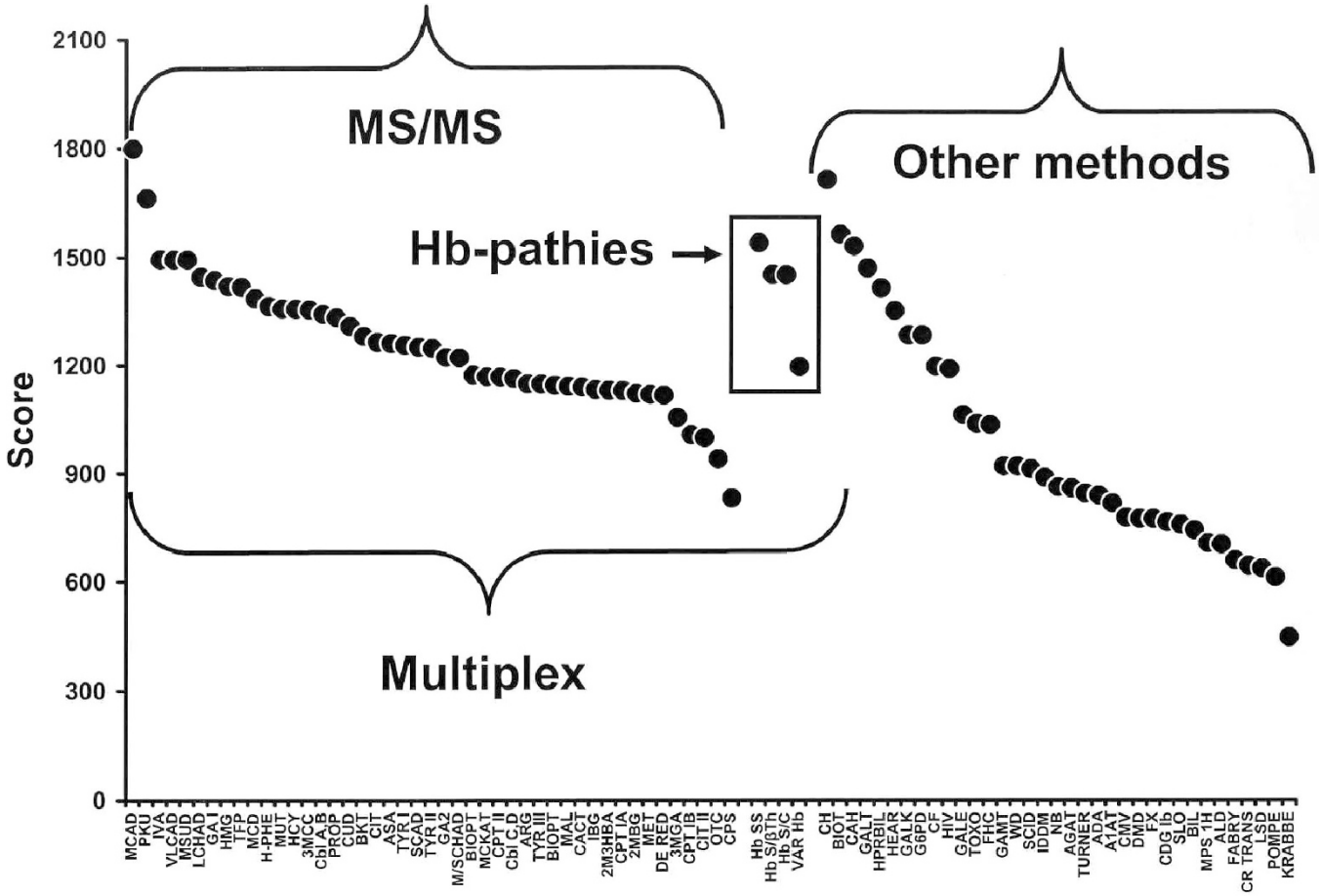



**Fig. 5.** Survey scores sorted by testing platforms

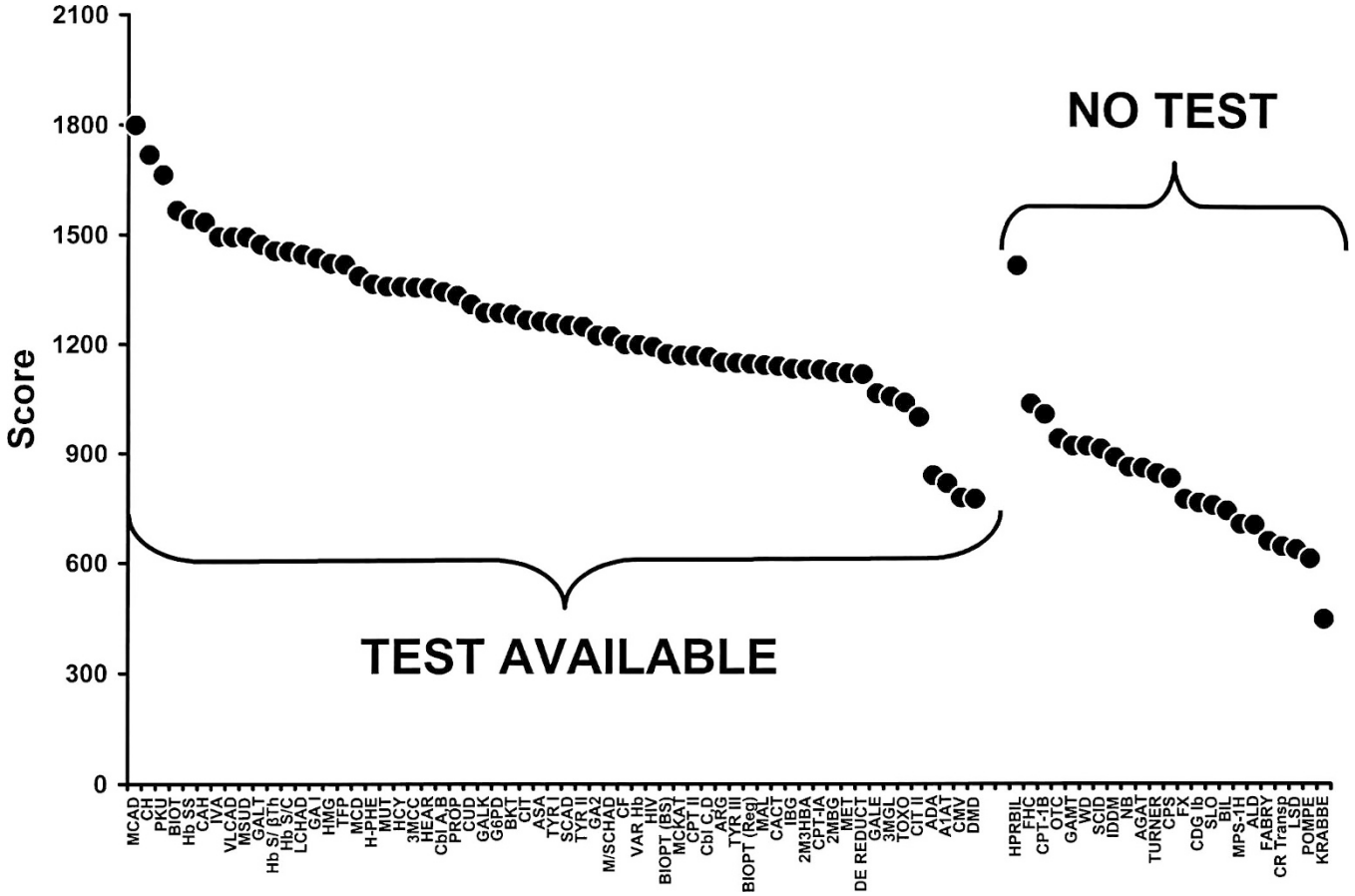



**Fig. 6** Scores by test availability (test/no test)

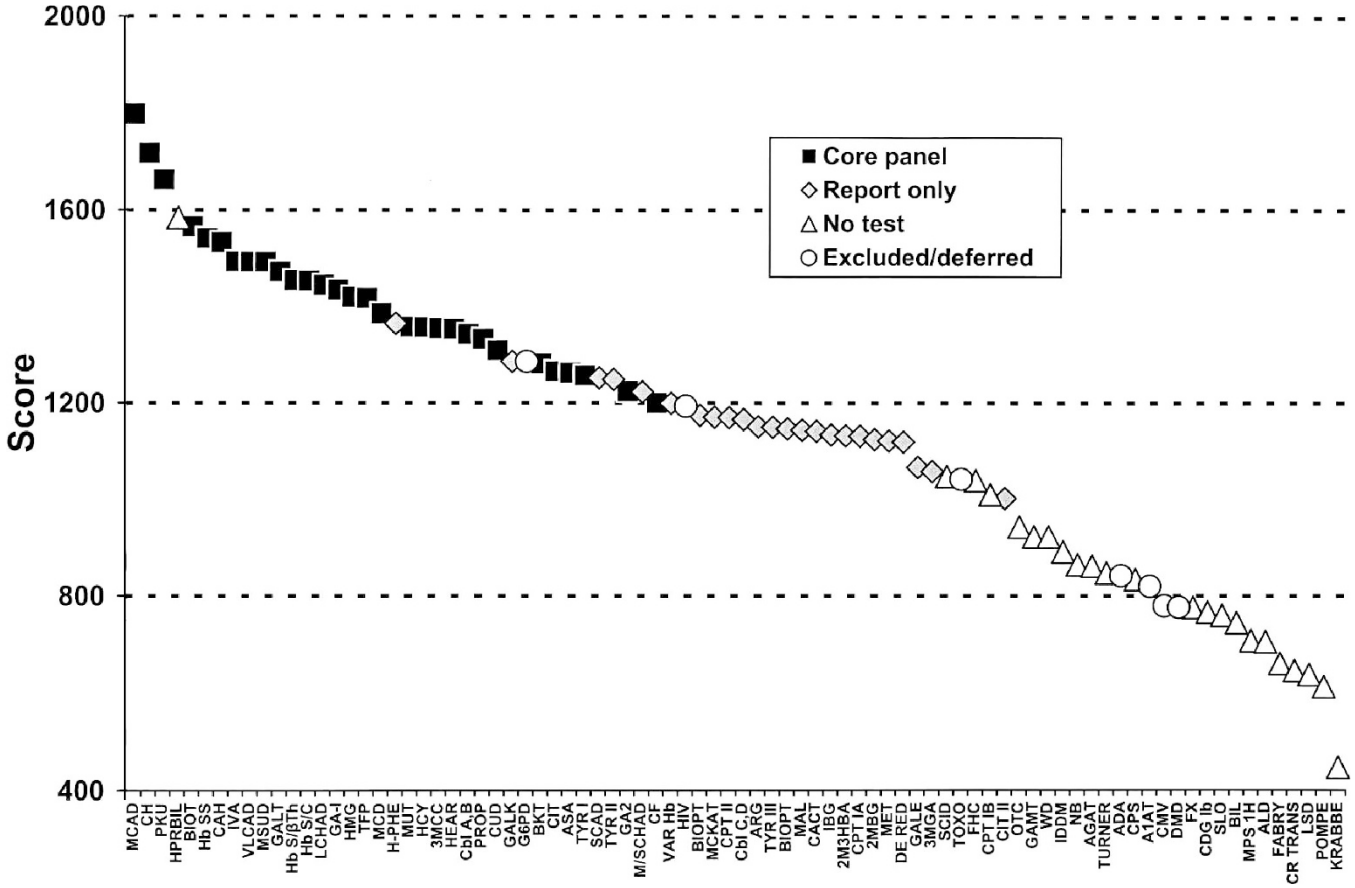



**Fig. 7.** Scores for all conditions distinguished by screening panel category

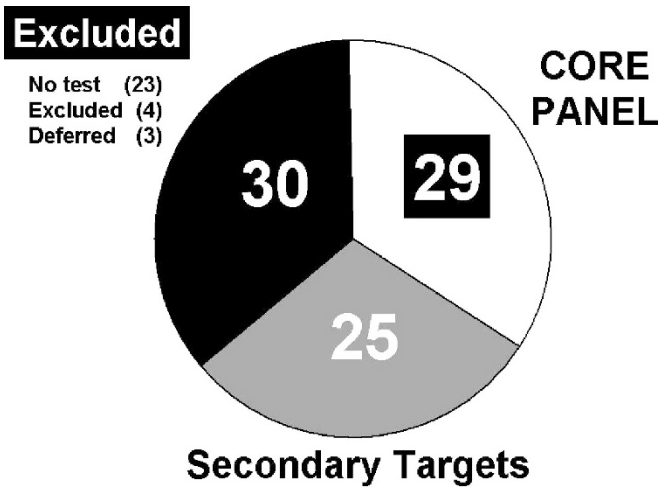



**Fig. 8.** Distribution of conditions into screening panel categories

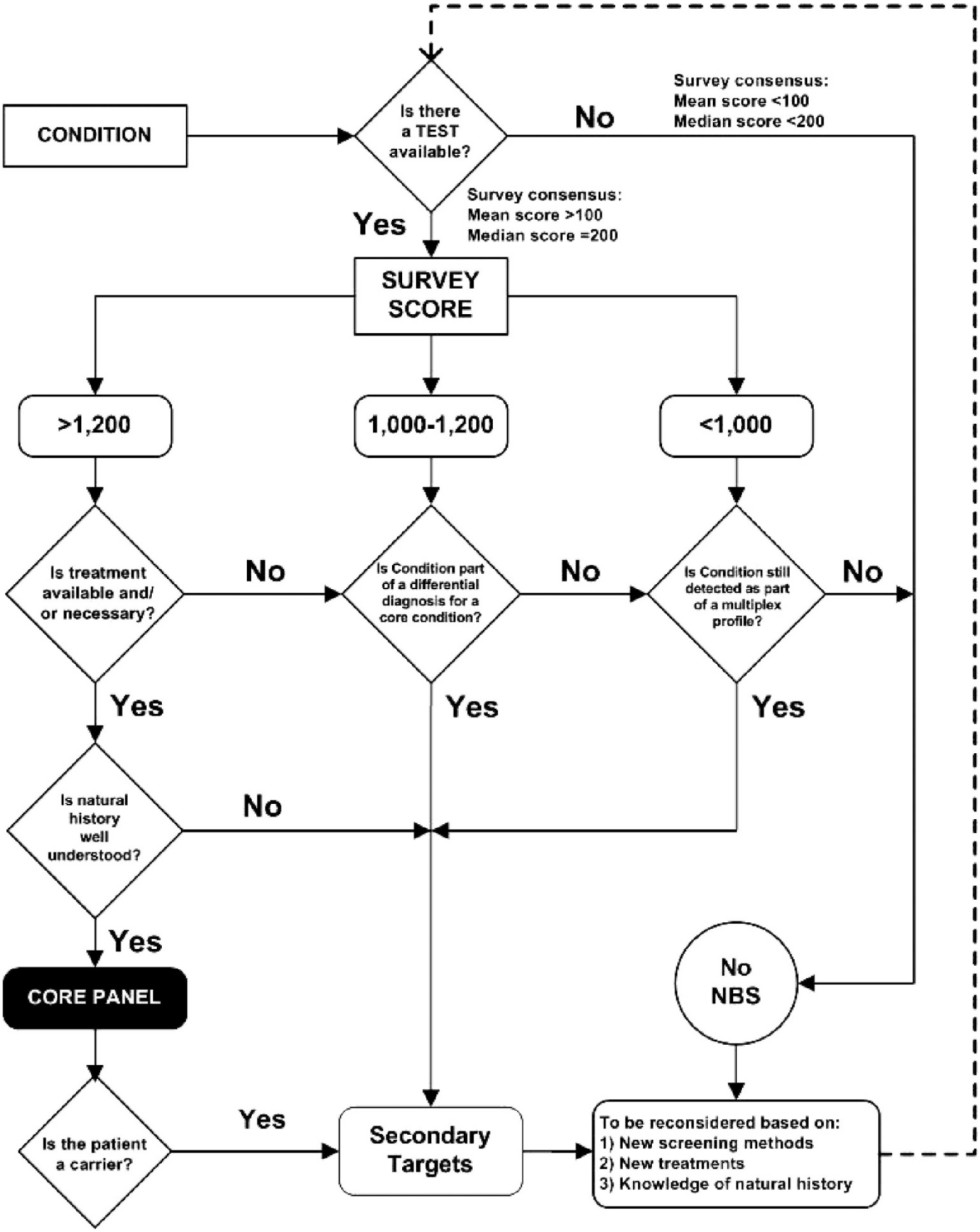



**Fig. 9.** Survey scores sorted by testing platforms

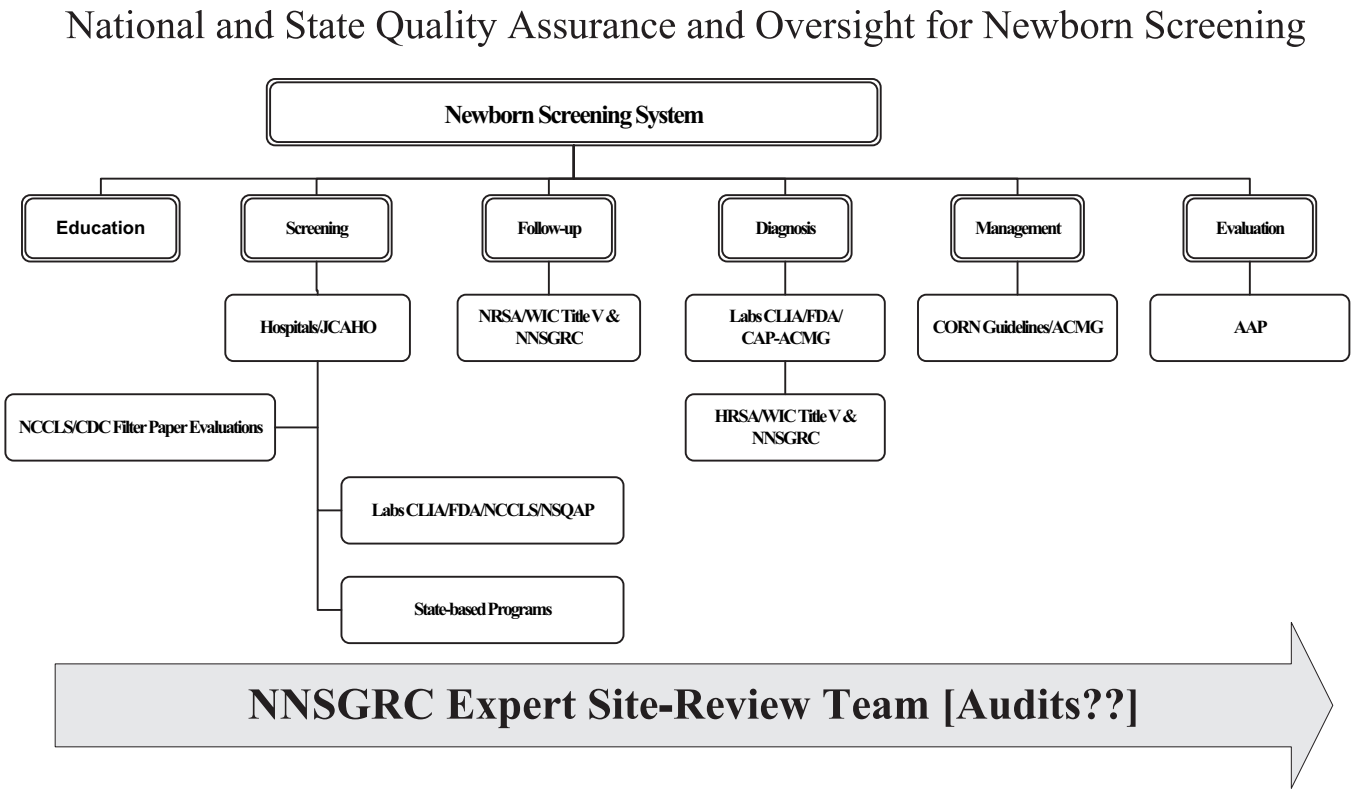



**Fig. 10.** National state quality assurance and oversight for newborn screening program components

## APPENDIX 1: Newborn screening fact sheet validation

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) | | | |
|---|---|---|---|---|---|
| | | Condition | Test | Diagnosis | Treatment |
| **Endocrine Disorders** | | | | | |
| Congenital adrenal hyperplasia | Maria I. New, MD<br>Cornell University<br>New York, NY | 1 | 1 | 1 | 1 |
| | Phyllis Speiser, MD<br>New York Univ. Med Center<br>Schneider Children's Hospital<br>Long Island Jewish Health System<br>New York, NY | 3 | 3 | 3 | 1 |
| Congenital hypothyroidism | Phyllis Speiser, MD<br>New York Univ. Med Center<br>Schneider Children's Hospital<br>Long Island Jewish Health System<br>New York, NY | 1 | 1 | 1 | 1 |
| | Marvin Mitchell, MD<br>New England Newborn Screening Program<br>University of Massachusetts Medical School<br>Jamaica Plain, MA | 1 | 1 | 1 | 1 |
| Type 1 diabetes mellitus (IDDM) | Marian Rewers, MD<br>University of Colorado School of Medicine<br>Denver, CO | | 1 | 1 | 1 |
| | William Tamborlane, MD<br>Yale University<br>New Haven, CT | 1 | 2 | 2 | 1 |
| | Charles Stanley, MD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 1 | 2 | 2 | 2 |
| **Carbohydrate Disorders** | | | | | |
| Classic galactosemia (GALT deficiency) | Louis B. Elsas, MD<br>University of Miami<br>Miami, FL | 4 | 4 | 4 | 4 |
| | Gerard Berry, MD<br>Jefferson Medical College<br>Philadelphia, PA | 3 | 2 | 1 | 3 |
| Galactokinase deficiency | Louis B. Elsas, MD<br>University of Miami<br>Miami, FL | 4 | 4 | 4 | 4 |
| | Gerard Berry, MD Jefferson Medical College<br>Philadelphia, PA | 4 | 2 | 2 | 4 |
| Galactose epimerase deficiency | Louis B. Elsas, MD<br>University of Miami<br>Miami, FL | 4 | 4 | 4 | 4 |
| | Gerard Berry, MD<br>Jefferson Medical College<br>Philadelphia, PA | 4 | 2 | 2 | 4 |
| Congenital disorder of glycosylation type 1b | Marc Patterson, MD, FRACP<br>Columbia University<br>New York, NY | 4 | 4 | 4 | 4 |
| | Donna Krasnewich, MD, PhD<br>National Human Genome Research Institute<br>Bethesda, MD | 1 | 4 | 1 | 2 |
| **Primary Immunodeficiencies** | | | | | |
| Adenosine deaminase Deficiency | Rebecca Buckley, MD<br>Duke University Medical Center<br>Durham, NC | 2 | N/A | 1 | 1 |
| | Jennifer Puck, MD<br>National Human Genome Research Institute<br>Bethesda, MD | 2 | N/A | 2 | 2 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) | | | |
|---|---|---|---|---|---|
| | | Condition | Test | Diagnosis | Treatment |
| Severe combined Immunodeficiency | Rebecca Buckley, MD<br>Duke University Medical Center<br>Durham, NC | 1 | N/A | 1 | 1 |
| | Jennifer Puck, MD<br>National Human Genome Research Institute<br>Bethesda, MD | 1 | N/A | 1 | 1 |
| **Other Genetic and Non-Genetic Conditions** | | | | | |
| $\alpha$-1-antitrypsin deficiency | Diane Cox, PhD<br>University of Alberta<br>Edmonton, Alberta, Canada | 1 | 1 | | |
| Biliary atresia | Deborah K. Freese, MD<br>Mayo Clinic College of Medicine<br>Rochester, MN | 2 | 3 | 2 | 3 |
| | Ronald J. Sokol, MD<br>University of Colorado School of Medicine<br>Denver, CO | 2 | 3 | 3 | 3 |
| Biotinidase deficiency | Barry Wolf, MD, PhD<br>Connecticut Children's Medical Center<br>Hartford, CT | 2 | 2 | 2 | 2 |
| | E. Regula Baumgartner, MD<br>University Children's Hospital<br>Basel, Switzerland | 2 | 1 | 1 | 2 |
| | Matthias Baumgartner, MD<br>University Children's Hospital<br>Zurich, Switzerland | 2 | 1 | 1 | 2 |
| Cystic fibrosis | Phillip Farrell, MD, PhD<br>University of Wisconsin<br>Madison, WI | 1 | 1 | 2 | 3 |
| | Garry R. Cutting, MD<br>Johns Hopkins University School of Medicine<br>Baltimore, MD | 1 | 3 | | 2 |
| Duchenne (DMD)/Becker muscular dystrophy (BMD) | Jon A. Wolff, MD<br>University of Wisconsin<br>Madison, WI | 2 | 2 | 2 | 2 |
| | R. Rodney Howell, MD<br>University of Miami<br>Miami, FL | 1 | 2 | 2 | 1 |
| Familial hypercholesterolemia (heterozygote) | Joseph P. McConnell, PhD<br>Mayo Clinic College of Medicine<br>Rochester, MN | 2 | 2 | 1 | 2 |
| | David Wilcken, MD<br>Prince of Wales Hospital<br>Randwick, NSW, Australia | 1 | 1 | 1 | 1 |
| Fragile X syndrome | Stephen Warren, PhD<br>Emory University<br>Atlanta, GA | 1 | N/A | 1 | 1 |
| | W. Ted Brown, MD, PhD<br>New York State Institute for Basic Research<br>Staten Island, NY | 2 | 2 | 2 | 3 |
| Hearing Loss | Cynthia C. Morton, PhD<br>Brigham and Women's Hospital<br>Harvard Medical School<br>Boston, MA | 1 | 1 | 2 | 2 |
| | Richard Smith, MD<br>University of Iowa Medical School<br>Iowa City, IA | 1 | 1 | 1 | 1 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) | | | |
|---|---|---|---|---|---|
| | | Condition | Test | Diagnosis | Treatment |
| Hyperbilirubinemia (kernicterus) | Jeffery Maisels, MD<br>William Beaumont Hospital<br>Royal Oak, MI | 3 | 3 | 3 | 3 |
| | Vinod Bhutani, MD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 3 | 3 | 3 | 3 |
| Neuroblastoma | Garrett Brodeur, MD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 1 | 1 | 1 | 1 |
| | Eizo Hiyama, MD<br>Hiroshima University Hiroshima, Japan<br>and<br>Hiroshi Naruse, MD<br>Quality Control Center for Mass Screening<br>Tokyo, Japan | 2 | 3 | 2 | 3 |
| Smith-Lemli–Opitz syndrome | Robert Steiner, MD<br>Oregon Health Science University<br>Portland, OR | 1 | 2 | 2 | 2 |
| | Mira Irons, MD<br>Children's Hospital<br>Harvard Medical School<br>Boston, MA | 1 | 1 | 1 | 3 |
| | Richard I. Kelley, MD, PhD<br>Johns Hopkins Medical Institution<br>Baltimore, MD | 4 | 2 | 2 | 1 |
| Turner syndrome | Virginia P. Sybert, MD<br>Univ. of Washington<br>Seattle, WA | 3/4 | 3/4 | 3/4 | 3/4 |
| | Ron G Rosenfeld, MD<br>Lucille Packard Foundation for Children<br>Palo Alto, CA | 1 | 3 | 3 | 2 |
| Wilson disease | Benjamin Shneider, MD<br>New York University Medical School<br>New York, NY | 3 | 3 | 2 | 2 |
| | Sihoun Haun, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester, MN | 1 | 2 | 2 | 1 |
| X-Linked Adrenoleukodystrophy | Hugo Moser, MD<br>Kennedy Krieger Institute<br>Johns Hopkins University<br>Baltimore, MD | 2 | 2 | 2 | 2-3 |
| | Robert Steiner, MD<br>Oregon Health Science University<br>Portland, OR | 2 | 2 | 2 | 3 |
| **Amino Acid Disorders** | | | | | |
| Argininemia | Stephen D. Cederbaum, MD<br>Mental Retardation Research Center, UCLA<br>Los Angeles, CA | 3 | 3 | 3 | 3 |
| | Mendel Tuchman, MD<br>Children's National Medical Center<br>Washington, DC | 4 | 4 | 4 | 4 |
| Argininosuccinic acidemia | Stephen D. Cederbaum, MD<br>Mental Retardation Research Center, UCLA<br>Los Angeles, CA | 1 | 3 | 1 | 3 |
| | Mendel Tuchman, MD<br>Children's National Medical Center<br>Washington, DC | 3 | 3 | 3 | 3 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) | | | |
|---|---|---|---|---|---|
| | | Condition | Test | Diagnosis | Treatment |
| Defects of biopterin cofactor biosynthesis | Nenad Blau, PhD<br>University Children's Hospital<br>University of Zurich<br>Zurich, Switzerland | 2 | 2 | 2 | 3 |
| | Harvey Levy, MD<br>Harvard Medical School<br>Boston, MA | 2 | 2 | 2 | 2 |
| Defects of biopterin cofactor regernation | Nenad Blau, PhD<br>University Children's Hospital<br>University of Zurich<br>Zurich, Switzerland | 2 | 2 | 2 | 3 |
| | Harvey Levy, MD<br>Harvard Medical School<br>Boston, MA | 3 | 2 | 2 | 4 |
| Carbamylphosphate synthetase deficiency | Mendel Tuchman, MD<br>Children's National Medical Center<br>Washington, DC | 3 | 3 | 3 | 3 |
| | Mark L. Batshaw, MD<br>Children's National Medical Center<br>George Washington University<br>Washington, DC | 3 | 3 | 3 | 3 |
| Citrullinemia(arginosuccinate synthase deficiency) | Mendel Tuchman, MD<br>Children's National Medical Center<br>Washington, DC | 3 | 3 | 3 | 3 |
| | Mark L. Batshaw, MD<br>Children's National Medical Center<br>George Washington University<br>Washington, DC | 3 | 3 | 3 | 3 |
| Citrullinemia type II (citrin deficiency) | Mendel Tuchman, MD<br>Children's National Medical Center<br>Washington, DC | 3 | 3 | | 3 |
| | Toshihiro Ohura, MD<br>Tohoku University School of Medicine<br>Sendai, Japan | 3 | 2 | 2 | 3 |
| | Mark L. Batshaw, MD<br>Children's National Medical Center<br>George Washington University<br>Washington, DC | 3 | 3 | 3 | 3 |
| Homocystinuria(cystathionine $\beta$-synthase deficiency) | S. Harvey Mudd, MD<br>NIH/NIMH<br>Bethesda, MD | 1 | 1 | 1 | 4 |
| | Vivian Shih, MD<br>Harvard Medical School<br>Boston, MA | 1 | | 3 | 3 |
| Hypermethioninemia(MAT 1/III deficiency) | S. Harvey Mudd, MD<br>NIH/NIMH<br>Bethesda, MD | 1 | 1 | 1 | 4 |
| | Vivian Shih, MD<br>Harvard Medical School<br>Boston, MA | 1 | 1 | 1 | 4 |
| Maple syrup (urine) disease | Louis B. Elsas, MD<br>University of Miami<br>Miami, FL | 3 | 3 | 1 | 3 |
| | Vivian Shih, MD<br>Harvard Medical School<br>Boston, MA | 1 | 1 | 1 | 4 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) Condition | Test | Diagnosis | Treatment |
|---|---|---|---|---|---|
| Ornithine transcarbamylase deficiency | Mendel Tuchman, MD<br>Children's National Medical Center<br>Washington, DC | 3 | 3 | 3 | 3 |
| | Mark L. Batshaw, MD<br>Children's National Medical Center<br>George Washington University<br>Washington, DC | 3 | 3 | 3 | 3 |
| Phenylketonuria (phenylalanine hydroxylase deficiency) | Nenad Blau, PhD<br>University Children's Hospital<br>University of Zurich<br>Zurich, Switzerland | 2 | 2 | 2 | 2 |
| | Harvey Levy, MD<br>Harvard Medical School<br>Boston, MA | 2 | 2 | 2 | 2 |
| | Vivian Shih, MD<br>Harvard Medical School<br>Boston, MA | 1 | 1 | 2 | 4 |
| Tyrosinemia type I (hepatorenal tyrosinemia) | C. Ronald Scott, MD<br>University of Washington<br>Seattle, WA | 2 | 3 | 1 | 2 |
| | Grant Mitchell, MD<br>Hospital Sainte-Justine<br>Montreal, Quebec, Canada | 2 | 2/3 | 1 | 2 |
| Tyrosinemia type II (oculocutaneous tyrosinemia) | C. Ronald Scott, MD<br>University of Washington<br>Seattle, WA | 2 | 3 | 2 | 2 |
| | Grant Mitchell, MD<br>Hospital Sainte-Justine<br>Montreal, Quebec, Canada | 2 | 4 | 2 | 2 |
| Tyrosinemia type III | C. Ronald Scott, MD<br>University of Washington<br>Seattle, WA | 3 | 3 | 3 | 4 |
| | Grant Mitchell, MD<br>Hospital Sainte-Justine<br>Montreal, Quebec, Canada | 4 | 4<br>(sensitivity)<br>1<br>(technical) | 4 | 4 |
| **Fatty Acid Oxidation Defects** | | | | | |
| Carnitine: acylcarnitine translocase deficiency | Nicola Longo, MD, PhD<br>University of Utah<br>Salt Lake City, UT | 2 | 2 | 1 | 2 |
| | Charles Stanley, MD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 3 | 3 | 2 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 3 | 3 | 2 | 4 |
| Carnitine palmitoyltransferase I deficiency (CPT1a) | Michael Bennett, PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 3 | 4 | 3 | 4 |
| | Cary Harding, MD<br>Oregon Health Sciences University<br>Portland, OR | | | | |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 4 | 4 | 4 | 4 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) Condition | Test | Diagnosis | Treatment |
|---|---|---|---|---|---|
| Carnitine palmitoyltransferase II deficiency | Michael Bennett, PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 2 | 4 | 4 | 3 |
| | Georgirene D. Vladutiu, PhD<br>Children's Hospital<br>Buffalo, NY | 4 | 2 | 4 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 2 | 3 | 2 | 4 |
| Carnitine uptake deficiency(Systemic) | Nicola Longo, MD, PhD<br>University of Utah<br>Salt Lake City, UT | 1 | 1 | 1 | 1 |
| | Charles Stanley, MD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 4 | 3 | 3 | 4 |
| Dienoyl-CoA reductase deficiency | Gerard Vockley, MD, PhD<br>Children's Hospital Pittsburgh<br>University of Pittsburgh<br>Pittsburgh, PA | 4 | 4 | 4 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 4 | 4 | 4 | 4 |
| Glutaric acidemia type II | Stephen I. Goodman, MD<br>University of Colorado Health Science Center<br>Denver, CO | 4 | 4 | 2 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 3 | 3 | 3 | 4 |
| | William J. Rhead, MD, PhD<br>Medical College of Wisconsin<br>Madison, WI | 2 | 2 | 2 | 4 |
| Long-chain 3-OH acyl-CoA dehydrogenase deficiency | Michael Bennett, PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 3 | 3 | 3 | 3 |
| | Arnold Strauss, MD<br>Vanderbilt University School of Medicine<br>Nashville, TN | 2 | 3 | 3 | 2 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 3 | 2 | 2 | 3 |
| Medium-chain acyl-CoA dehydrogenase deficiency | Arnold Strauss, MD<br>Vanderbilt University School of Medicine<br>Nashville, TN | 2 | 2 | 2 | 2 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 2 | 1 | 1 | 1 |
| Medium/short-chain 3-OH acyl-CoA dehydrogenase deficiency | Arnold Strauss, MD<br>Vanderbilt University School of Medicine<br>Nashville, TN | 4 | 4 | 4 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 4 | 4 | 4 | 4 |
| Medium–chain ketoacyl-CoA thiolase deficiency | Michael Bennett,PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 4 | 4 | 4 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 4 | 4 | 4 | 4 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) Condition | Test | Diagnosis | Treatment |
|---|---|---|---|---|---|
| Short-chain acyl-CoA dehydrogenase deficiency | Gerard Vockley, MD, PhD<br>Children's Hospital Pittsburgh<br>University of Pittsburgh<br>Pittsburgh, PA | 2 | 1 | 1 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 4 | 3 | 2 | 4 |
| | Dietrich Matern, MD<br>Mayo Clinic College of Medicine<br>Rochester, MN | 2 | 1 | 1 | 2 |
| Trifunctional protein deficiency | Arnold Strauss, MD<br>Vanderbilt Univeristy School of Medicine<br>Nashville, TN | 3 | 3 | 3 | 3 |
| | Michael Bennett, PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 4 | 4 | 4 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 3 | 2 | 2 | 3 |
| Very long-chain acyl-CoA dehydrogenase deficiency | Arnold Strauss, MD<br>Vanderbilt University School of Medicine<br>Nashville, TN | 2 | 2 | 2 | 2 |
| | Michael Bennett, PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 3 | 3 | 3 | 4 |
| | Piero Rinaldo, MD, PhD<br>Mayo Clinic College of Medicine<br>Rochester MN | 3 | 2 | 2 | 3 |
| **Organic Acidurias** | | | | | |
| 2-methylbutyryl-CoA dehydrogenase deficiency | Gerard Vockley, MD, PhD<br>Children's Hospital Pittsburgh<br>University of Pittsburgh<br>Pittsburgh, PA | 1 | 1 | 1 | 4 |
| | Dietrich Matern, MD<br>Mayo Clinic College of Medicine<br>Rochester, MN | 2 | 1 | 1 | 2 |
| 2-methyl 3-hydroxybutyric-aciduria | Michael Bennett, PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 4 | 4 | 4 | 4 |
| | Dietrich Matern, MD<br>Mayo Clinic College of Medicine<br>Rochester, MN | 3 | 4 | 3 | 3 |
| | Regina Ensenauer, MD<br>Von Haunershes Kinderspital<br>Ludwig-Maximilians-University<br>Munich, Germany | 4 | 4 | 4 | 4 |
| 3-hydroxy 3-methyl glutaric aciduria (HMG) | Pinar Ozand, MD, PhD<br>King Faisal Specialist Hospital and Research Centre<br>Riyadh, Saudi Arabia | 4 | 1 | 1 | 1 |
| | Grant Mitchell, MD<br>Hospital Sainte-Justine<br>Montreal, Quebec, Canada | 2 | 4 | 2 | 3 |
| 3-Methylglutaconic Aciduria (Type 1-hydrotase deficiency) | Robert Steiner, MD<br>Oregon Health University<br>Portland, OR | 2 | 2 | 2 | 2 |
| | Richard I. Kelley, MD, PhD<br>Johns Hopkins Medical Institution<br>Baltimore, MD | 4 | 2 | 2 | 4 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) | | | |
|---|---|---|---|---|---|
| | | Condition | Test | Diagnosis | Treatment |
| 3-methylcrotonyl-CoA carboxylase deficiency | Matthias Baumgartner, MD<br>University Children's Hospital<br>Zurich, Switzerland | 2 | 1 | 2 | 4 |
| | Richard I. Kelley, MD, PhD<br>Johns Hopkins Medical Institution<br>Baltimore, MD | 4 | 2 | 2 | 4 |
| ß-ketothiolase deficiency | Michael Bennett, PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 4 | 4 | 4 | 4 |
| | Toshiyuki Fukao, MD<br>Gifu University School of Medicine<br>Gifu, Japan | 3 | 3 | 3 | 3 |
| Glutaric cademia type 1 | Stephen I. Goodman, MD<br>University of Colorado Health Science Center<br>Denver, CO | 2 | 2 | 2 | 3 |
| | Pinar Ozand, MD, PhD<br>King Faisal Specialist Hospital and Research Centre<br>Riyadh, Saudi Arabia | 2 | 2 | 2 | 3 |
| Isobutyryl-CoA dehydrogenase Deficiency | Gerard Vockley, MD, PhD<br>Children's Hospital Pittsburgh<br>University of Pittsburgh<br>Pittsburgh, PA | 3 | 1 | 1 | 4 |
| | Dietrich Matern, MD<br>Mayo Clinic College of Medicine<br>Rochester, MN | 2 | 2 | 1 | 3 |
| Isovaleric acidemia | Gerard Vockley, MD, PhD<br>Children's Hospital Pittsburgh<br>University of Pittsburgh<br>Pittsburgh, PA | 1 | 1 | 1 | 3 |
| | Dietrich Matern, MD<br>Mayo Clinic College of Medicine<br>Rochester, MN | 1 | 1 | 1 | 1 |
| | Regina Ensenauer, MD<br>Von Haunershes Kinderspital<br>Ludwig-Maximilians-University<br>Munich, Germany | 1 | 1 | 1 | 3 |
| Malonic acidemia | Michael Bennett, PhD<br>Children's Hospital of Philadelphia<br>Philadelphia, PA | 4 | 4 | 4 | 4 |
| | Pinar Ozand, MD, PhD<br>King Faisal Specialist Hospital and Research Centre<br>Riyadh, Saudi Arabia | 4 | 4 | 4 | 4 |
| Methylmalonic acidemia (CblA,B) | David Rosenblatt, MD<br>McGill University<br>Montreal, Quebec, CA | 4 | 4 | 4 | 4 |
| | William Nyhan, MD, PhD<br>University of California, San Diego<br>La Jolla, CA | 2 | 1 | 1 | 2 |
| Methylmalonic acidemia (Cbl C,D) | David Rosenblatt, MD<br>McGill University<br>Montreal, Quebec, CA | 4 | 4 | 4 | 4 |
| | William Nyhan, MD, PhD<br>University of California, San Diego<br>La Jolla, CA | 2 | 1 | 1 | 2 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) | | | |
|---|---|---|---|---|---|
| | | Condition | Test | Diagnosis | Treatment |
| Methylmalonic acidemia (Mutase deficiency) | David Rosenblatt, MD<br>McGill University<br>Montreal, Quebec, CA | 4 | 4 | 4 | |
| | William Nyhan, MD, PhD<br>University of California, San Diego<br>La Jolla, CA | 2 | 1 | 1 | 2 |
| Holocarboxylase synthetase deficiency | Barry Wolf, MD, PhD<br>Connecticut Children's Medical Center<br>Hartford, CT | 3 | 3 | 3 | 3 |
| | E. Regula Baumgartner, MD<br>University Children's Hospital<br>Basel, Switzerland | 2 | 2 | 2 | 2 |
| | Matthias Baumgartner, MD<br>University Children's Hospital<br>Zurich, Switzerland | 2 | 2 | 2 | 2 |
| Propionyl-CoA carboxylase deficiency | Pinar Ozand, MD, PhD<br>King Faisal Specialist Hospital and Research Centre<br>Riyadh, Saudi Arabia | 3 | 1 | 1 | 1 |
| | William Nyhan, MD, PhD<br>University of California, San Diego<br>La Jolla, CA | 2 | 1 | 1 | 2 |
| **Hematology/Hemoglobinopathies** | | | | | |
| Sickle cell anemia (Hb SS disease) | Carolyn Hoppe, MD<br>Children's Hospital Oakland<br>Oakland, CA | 1 | 2 | 1 | 1 |
| | Elliott Vichinsky, MD<br>Children's Hospital Oakland<br>Oakland, CA | 1 | 2 | 1 | 1 |
| Hemoglobin SC | Carolyn Hoppe, MD<br>Children's Hospital Oakland<br>Oakland, CA | 1 | 2 | 1 | 1 |
| | Elliott Vichinsky, MD<br>Children's Hospital Oakland<br>Oakland, CA | 1 | 2 | 1 | 1 |
| Hemoglobin S/beta-thalassemia (Hb Sß-thal) | Carolyn Hoppe, MD<br>Children's Hospital Oakland<br>Oakland, CA | 1 | 2 | 1 | 1 |
| | Elliott Vichinsky, MD<br>Children's Hospital Oakland<br>Oakland, CA | 1 | 2 | 1 | 1 |
| Variant hemoglobinopathies (including HbE) | Carolyn Hoppe, MD<br>Children's Hospital Oakland<br>Oakland, CA | 1 | 2 | 1 | 1 |
| | Elliott Vichinsky, MD<br>Children's Hospital Oakland<br>Oakland, CA | 1 | 2 | 1 | 1 |
| Glucose-6-phosphate dehydrogenase deficiency (G6PD) | Ernest Beutler, MD<br>Scripps Research Institute<br>La Jolla, CA | 3 | 1 | 2 | 4 |
| | Carolyn Hoppe, MD<br>Children's Hospital Oakland<br>Oakland, CA | 2 | 2 | 1 | 4 |

| CONDITION | VALIDATED BY | EVIDENCE LEVELS (1-4) | | | |
|---|---|---|---|---|---|
| | | Condition | Test | Diagnosis | Treatment |
| **Creatine Metabolism Disorders** | | | | | |
| Guanidinoacetate methyltransferase deficiency (GAMT) | William O'Brien, PhD<br>Baylor College of Medicine<br>Dallas, TX | 4 | 4 | 4 | 4 |
| | Robert Steiner, MD<br>Oregon Health Science University<br>Portland, OR | 4 | 4 | 4 | 4 |
| Arginine:glycine amidinotransferase deficiency(AGAT) | William O'Brien, PhD<br>Baylor College of Medicine<br>Dallas, TX | 4 | 4 | 4 | 4 |
| | Robert Steiner, MD<br>Oregon Health Science University<br>Portland, OR | 4 | 4 | 4 | 4 |
| Creatine transporter defect | William O'Brien, PhD<br>Baylor College of Medicine<br>Dallas, TX | 4 | 4 | 4 | 4 |
| | Robert Steiner, MD<br>Oregon Health Science University<br>Portland, OR | 4 | 4 | 4 | 4 |
| **Lysosomal Storage Disorders** | | | | | |
| Fabry disease | Gregory A. Grabowski, MD<br>Cincinnati Children's Hospital<br>Medical Center<br>Cincinnati, OH | 2 | 3 | 3 | 1 |
| | Robert J. Desnick, MD, PhD<br>Mount Sinai Medical Center<br>New York, NY | 2 | 3 | 4 | 1 |
| Krabbe disease | Gregory A. Grabowski, MD<br>Cincinnati Children's Hospital<br>Medical Center<br>Cincinnati, OH | 3 | 3 | 3 | 4 |
| Hurler, Scheie, Hurler-Scheie (MPS I) | Gregory A. Grabowski, MD<br>Cincinnati Children's Hospital<br>Medical Center<br>Cincinnati, OH | 3 | 3 | 4 | 2 |
| Pompe disease (glycogen storage disease type II) | Gregory A. Grabowski, MD<br>Cincinnati Children's Hospital<br>Medical Center<br>Cincinnati, OH | 4 | 3 | 3 | 3/4 |
| | R. Rodney Howell, MD<br>University of Miami<br>Miami, FL | 1 | 4 | 1 | 4 |

# ENDOCRINE DISORDERS

| CONDITION | Congenital adrenal hyperplasia |
|---|---|
| TYPE of DISORDER | Endocrinologic disorder, 21-hydroxylase deficiency |
| ETHNICITY | Panethnic but higher in Saudi Arabia, Yupik Alaskans and in La Reunion, lower in New Zealand. |
| SCREENING METHOD(S) | FIA |
| NBS STATUS in the US | Screened for in 37 of 51 states, 77% of annual births (August 2004) |

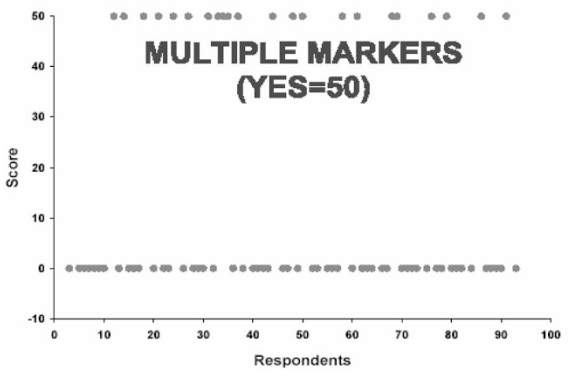
| Responses: | 93 | Valid scores: | 1,560 | 93% | PubMed references (August 2004): | 4,318 |
|---|---|---|---|---|---|---|

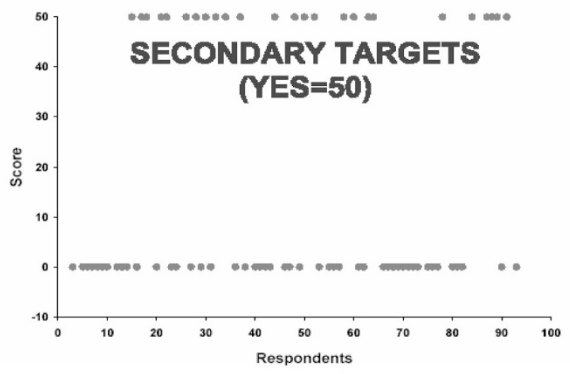
| Gene | *CYP21A2* | Locus | *6p21.3* | OMIM | *201910* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | |
|---|---|---|---|
| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
| The condition | | | |
| Incidence | >1:25,000 | 76% | Classical (21-OH deficiency) CAH = 1:18,987 in US newborn screening based on 13,347,888 newborns screened [1]. |
| Phenotype at birth | <50% of cases | 55% | Most females have ambiguous genitalia, if recognized. Males are usually undetected [2-4]. |
| Burden if untreated | Profound | 90% | 9% mortality, masculinization in females. Adrenocortical insufficiency in severe forms [3,4]. |
| The test | | | |
| Screening test | Yes | 94% | 17-OHP concentration by FIA (DELFIA, RIA, ELISA) [5,6]. Second tier testing by MS/MS [7-9], repeat RIA after two weeks or genotyping [10,11]. 90-95% have one of 9 common mutations in CYP21A2 [10]. |
| Doable in DBS or by physical method | Yes | 91% | Yes, see [5]. |
| High throughput | Yes | 73% | Yes, see [5]. |
| Overall cost <$1 | <$1/test | 58% | $3.00 per test [6,12]. |
| Multiple analytes | No (lack of consensus) (*) | 29% | Second tier testing of 17-OHP, androstenedione and cortisol by MS/MS [7-9]. |
| Secondary targets | No (lack of consensus) (*) | 34% | No. |
| Multiplex platform | No | 24% | No. |
| The treatment | | | |
| Availability & cost | Widely available | 91% | Pediatric endocrinologists are widely available. Neonatal detection allows steroid treatment and avoids acute adrenal crisis [2,8]. |
| Efficacy | Potential to prevent MOST negative consequences | 63% | Female masculinization begins in the prenatal period so not all sequelae are avoided; normal height may not be reached when treated [2,10]. |
| Early intervention | Clear evidence that early intervention optimizes outcome | 95% | Neonatal detection allows steroid treatment and avoids acute adrenal crisis [2,10,13]. |
| Early identification | Clear benefits to family and society | 95% | Identification of at risk family members and genetic counseling [10]. Prenatal diagnosis is available [16,17]. Molecular testing of CYP21A2 is available. |
| Mortality prevention | Yes | 99% | Mortality rates of 9% due to adrenal crises in neonates [6]. |
| Diagn. confirmation | Widely available | 87% | CYP21A2 mutation analysis has an 80 - 95% detection rate [11,18]. |
| Acute management | Widely available | 86% | Pediatric endocrinologists as part of a multidisciplinary team are widely available, though medical geneticists may be less available [8,15,17]. |
| Simplicity of therapy | No specialist involvement | 57% | Requires multidisciplinary team including pediatric endocrinologist, medical geneticist, pediatric urology/surgery, psychology [8]. |

**Congenital adrenal hyperplasia**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | FIA |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1533 /2100 | % of max score | 73% |
| Rank: | 0.93 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Congenital adrenal hyperplasia (21-hydroxylase deficiency) had one of the highest scores of the conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel. Introduction of biochemical and/or molecular 2nd tier tests are likely to improve the sensitivity and specificity of current primary screening methods [7, 8]. Screening is for the 21-hydroxylase form that accounts for 90% of CAH. False positives in premature infants and false negatives among nonsalt-wasting forms are limitations. Views differed between survey and literature on simplicity of therapy.

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| | |
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| CONDITION | Congenital hypothyroidism |
|---|---|
| TYPE of DISORDER | Endocrinologic disorder |
| ETHNICITY | Panethnic distribution. More common in Hispanic and Native Americans. |
| SCREENING METHOD(S) | RIA, ELISA |
| NBS STATUS in the US | Screened for in 51 of 51 states, 100% of annual births (August 2004) |

| Responses: | 84 | Valid scores: | 1,466 | 97% | PubMed references (August 2004): | 2,251 |
|---|---|---|---|---|---|---|

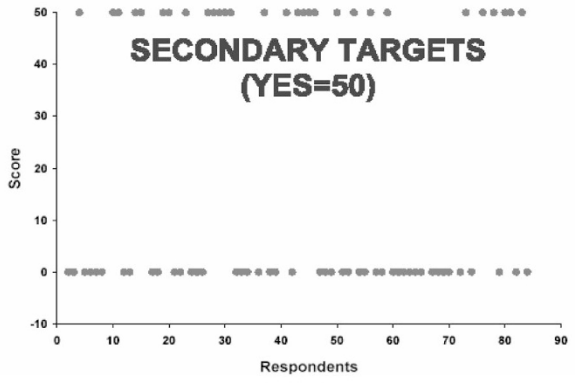
| Gene | *PAX8 TSHR DUOX2* | Locus | *2q12-q14 14q31 15q15.3* | OMIM | *218700; 275200; 607200* |
|---|---|---|---|---|---|

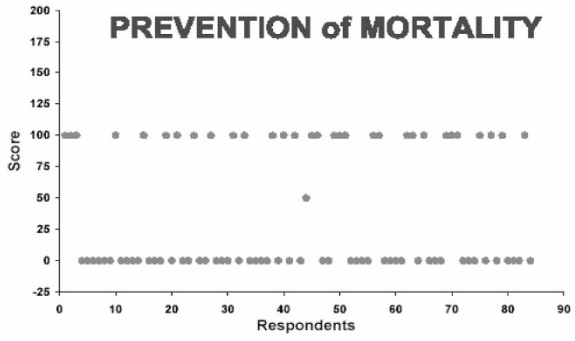
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:5,000 | 96% | 1:3,044 with primary hypothyroidism in US newborn screens of 40,214,946 newborns [1]. |
| Phenotype at birth | <25% of cases | 82% | About 1-5% are apparent at birth (jaundice, a nonspecific finding). Most protected by maternal thyroid hormone [2]. Usually presents after 3 months [3-5]. |
| Burden if untreated | Profound | 93% | Mental retardation (IQ = 80) and lowered subtest scores [3-7]. |
| The test | | | |
| Screening test | Yes | 100% | RIA for TSH (7 states) or both T4 and TSH (45 programs) [8-10]. |
| Doable in DBS or by physical method | Yes | 99% | Yes, see [8,9]. |
| High throughput | Yes | 78% | Yes, see [8,10]. |
| Overall cost <$1 | <$1/test | 65% | Overall costs vary with the use of TSH or T4 as a primary marker and the cutoffs that lead to secondary testing for TSH among those with low T4. [1,10]. |
| Multiple analytes | No | 36% | No, see [8]. |
| Secondary targets | No (lack of consensus) (*) | 39% | No, see [8]. |
| Multiplex platform | No | 27% | No, see [8]. |
| The treatment | | | |
| Availability & cost | Widely available | 98% | Pediatric endocrinologists are widely available. Primary care providers may choose to manage some cases [10]. |
| Efficacy | Potential to prevent ALL negative consequesces | 85% | Treatment resolves growth deficiency and significantly improves mental outcome [10-13]. |
| Early intervention | Clear evidence that early intervention optimizes outcomes | 98% | Treatment resolves growth deficiency and improves mental outcome [10-13]. |
| Early identification | Clear benefits to family and society | 99% | Genetic counseling available for heritable forms [14]. |
| Mortality prevention | No (lack of consensus) (*) | 38% | Not expected to be changed [10-14]. |
| Diagn. confirmation | Widely available | 100% | Pediatric endocrinologists are widely available and confirmatory algorithms are well established [10,11]. |
| Acute management | Widely available | 98% | Pediatric endocrinologists are widely available. Management guidelines are well established [10,16]. |
| Simplicity of therapy | Regular involvement of specialist | 94% | Thyroxine treatment and lifelong monitoring require pediatric endocrinologist involvement [15,17]. |

**Congenital hypothyroidism**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | FIA |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1728 /2100 | % of max score | 82% |
| Rank: | 0.99 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Congenital hypothyroidism had the second highest score of the panel of conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel. TSH is the most sensitive and specific marker for primary hypothyroidism, though is more expensive to test and is of limited value in identification of secondary and tertiary hypothyroidism and TBG deficiency. T4 as a primary marker followed by TSH fails to detect those with elevated TSH but normal T4.

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| | |
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| CONDITION | Insulin dependent diabetes mellitus |
|---|---|
| TYPE of DISORDER | Endocrinology |
| ETHNICITY | Panethnic but 20x higher in US than in China likely due to population-specific alleles [1]. |
| SCREENING METHOD(S) | No test available at this time |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | 51 | Valid scores: | 868 | 95% | PubMed references (August 2004) | 404546 |
|---|---|---|---|---|---|---|

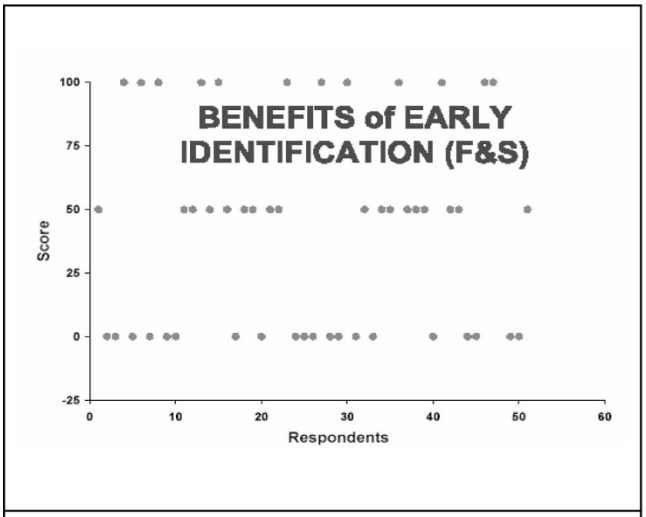
| Gene | *IDDM1* | Locus | *Xp11.23-q13.3*<br>*12q24.2*<br>*6p21.3* | OMIM | *222100* |
|---|---|---|---|---|---|

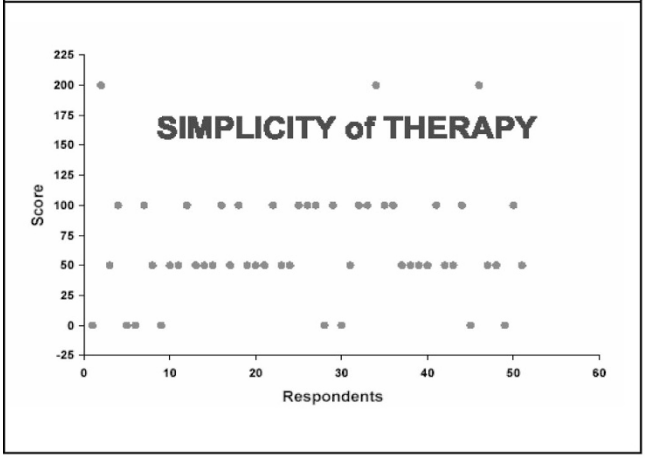
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:5,000 | 85% | 1:6,666 in people under 18 yrs of age [1,2,5]. |
| Phenotype at birth | Almost never | 95% | No autoantibody evidence during infancy; rarely present prior to 3 months [3]. Progression is variable [4]. |
| Burden if untreated | Profound | 82% | Diabetic ketoacidosis leading to death [5]. |
| The test | | | |
| Screening test | No | 14% | Screening test for predisposition to diabetes by HLA DR and DQ alleles is not validated in a large general population. [6] Second tier testing by radioimmunoassays for insulin, GAD, IC512bdc/IA-2 autoantibodies are highly predictive [7,8]. |
| Doable in DBS or by physical method | No | 21% | Not applicable. |
| High throughput | No | 23% | Not applicable, though autoantibodies for GAA, ICA512AA and MUAA would be high throughput [9]. |
| Overall cost <$1 | No (>$1/test) | 9% | Not applicable. |
| Multiple analytes | No | 14% | Not applicable. |
| Secondary targets | No | 7% | Not applicable. |
| Multiplex platform | No | 12% | Not applicable. |
| The treatment | | | |
| Availability & cost | Limited availability | 74% | No preventive treatment is available. Insulin and dietary management are required and available. Pancreatic transplants with immunosuppression in late disease continue to improve but are more limited availability [10-12]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 37% | Specific dietary treatments are investigative and transplants are improving [10-15]. Treatment leads to a transient delay in ß-cell destruction [16]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 26% | Treatment leads to a transient delay in ß-cell destruction. Specific dietary treatments are investigative and transplants are improving [10-15]. |
| Benefits of early identification | SOME benefits to family and society (lack of consensus) (*) | 43% | Identifies at-risk siblings [2]. |
| Prevention of mortality | No | 45% | Disease progression is slowed and mortality is reduced [10-12]. |
| Confirmation of diagnosis | Widely available | 83% | Hyperglyemia with relative insulin deficiency [17]. |
| Acute management | Widely available | 92% | Insulin [2,18]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 34% | Periodic involvement of specialists is needed [4,6]. |

**Insulin dependent diabetes mellitus**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 891 /2100 | % of max score | 42% |
| Rank: | 0.23 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Newborn screening for type I diabetes mellitus is in limited pilot testing to improve our understanding of the natural history of the condition and its relationship to possible environmental triggers that lead to autoantibody production. Potential screening tests are not yet validated in large general US populations. Neither the NIH prevention trial nor the European ENDIT Study showed that you could delay or prevent Type I DM in high risk subjects with family history and positive for autoantibodies.

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| | |
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# CARBOHYDRATE DISORDERS

| CONDITION | Classic galactosemia (GALT) |
|---|---|
| TYPE of DISORDER | Disorder of galactose metabolism |
| ETHNICITY | 1:23,500 in Ireland and 1:100,000 in Sweden. |
| SCREENING METHOD(S) | Microbiologic for G-1-P and galactose and fluorometric assays for GALT acitivity |
| NBS STATUS in the US | Screened for in 51 of 51 states, 100% of annual births (August 2004) |

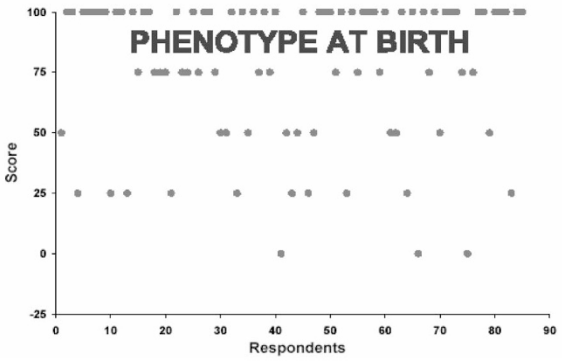
| Responses: | 85 | Valid scores: | 1,472 | 96% | PubMed references (August 2004) | 2,021 |
|---|---|---|---|---|---|---|

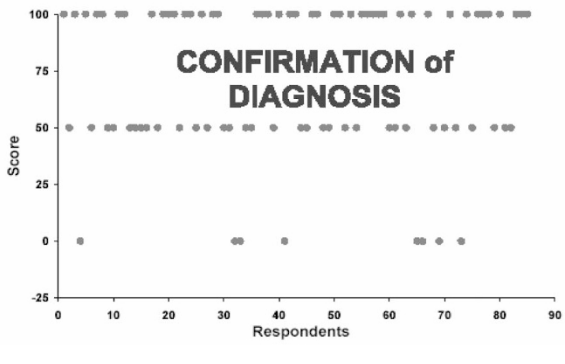
| Gene | *GALT* | Locus | *9p13* | OMIM | *230400* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:50,000 | 42% | 1:53,261 in US newborns from 35,897,634 newborn screens [1]. |
| Phenotype at birth | <25% of cases (lack of consensus) (*) | 76% | Majority of cases not identified in NBS manifest poor growth and feeding, and often jaundice [2-5]. |
| Burden if untreated | Profound | 91% | Bleeding diathesis and sepsis leading to shock and death. Usually fatal [2-5]. |
| The test | | | |
| Screening test | Yes | 99% | Beutler fluorescent spot screening test for GALT activity described in 1966 [6]. Gal-1-P and Gal levels are also screened by HPLC [7] in most states [1]. GALK is not identified if only the Beutler test is done. |
| Doable in DBS or by physical method | Yes | 100% | Yes, see [6,7]. |
| High throughput | Yes | 85% | Yes, see [6,7]. |
| Overall cost <$1 | <$1/test | 58% | No, single condition screening [6,7]. |
| Multiple analytes | No | 38% | Fluorescent spot assay and RBC Gal-1-P [6,7]. |
| Secondary targets | Yes | 49% | GALK and GALE are secondary targets of screening by galactose levels but not GALT activity [7]. |
| Multiplex platform | No | 21% | No. |
| The treatment | | | |
| Availability & cost | Widely available | 91% | Metabolic specialists for dietary management and monitoring are of limited availability [8-10]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 45% | Poor growth and feeding, lethargy, jaundiice, vomiting and hypotonia resolve with earliest treatment but long-term complications involving brain and ovaries (in females) occur in majority of cases [2,8-10]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 85% | Mortality significantly reduced [8,11]. |
| Benefits of early identification | Clear benefits to family and society | 88% | Genetic counseling, prenatal diagnosis and molecular testing are available [2,11]. |
| Prevention of mortality | Yes | 96% | Mortality significantly reduced [7]. |
| Confirmation of diagnosis | Yes (lack of consensus) (*) | 71% | Erythrocyte galactose-1-phosphate uridyl transferase activity and molecular testing [2,7,8]. |
| Acute management | Limited availability | 77% | Dietary management to remove galactose can prevent the life-threatening complications of classical galactosemia [2,4]. |
| Simplicity of therapy | Periodic involvement of specialist | 63% | Metabolic specialists for dietary management and monitoring are of limited availability [2]. |

**Classic galactosemia (GALT)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | Multiple |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1473 /2100 | % of max score | 70% |
| Rank: | 0.88 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

GALT is the primary target of galactosemia screening and is detected by screening for GALT activity and/or galactose and G-1-P levels. The inability of screening to improve long-term outcome for most patients, aside from reduction in mortality, has complicated arguments to screen for galactosemia. Earlier screening in the US is useful in finding additional cases that may die undiagnosed.

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| | |
|---|---|
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| CONDITION | Galactokinase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of galactose metabolism |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Microbiologic for G-1-P and galactose and fluorometric assays for GALT acitivity |
| NBS STATUS in the US | Screened for in 51 of 51 states, 100% of annual births (August 2004) |

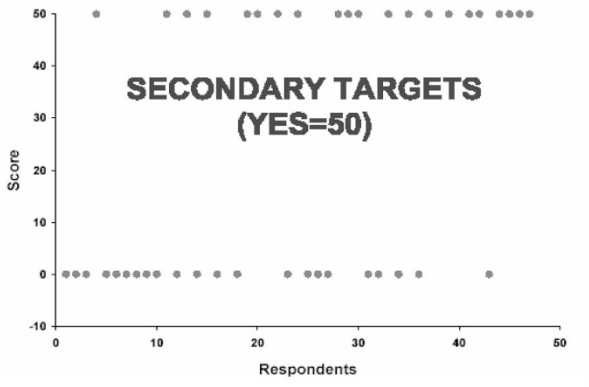
| Responses: | 47 | Valid scores: | 820 | 97% | PubMed references (August 2004) | 763 |
|---|---|---|---|---|---|---|

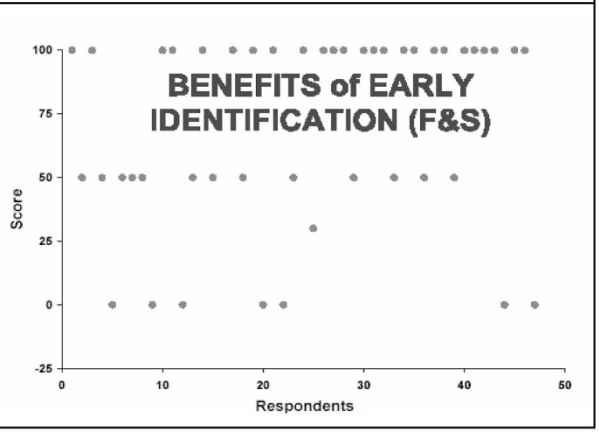
| Gene | *GALK1* | Locus | *17q24* | OMIM | *230200* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | >1:25,000 | 11% | Incidence is not known. Estimated at <1:100,000 [1]. |
| Phenotype at birth | Almost never | 83% | Cataracts have been reported as early as 4 weeks of age [2-4]. |
| Burden if untreated | Moderate | 52% | Cataracts are the only consistent clinical finding [2-4]. |
| The test | | | |
| Screening test | Yes | 86% | Beutler fluorescent spot screening test for GALT activity first described in 1966 [5] is normal. Gal-1-P and Gal levels are also screened by HPLC in most states [6]. RBC Gal-1-P and urinary galactitol are high. |
| Doable in DBS or by physical method | Yes | 93% | Yes, see [5,6]. |
| High throughput | Yes | 77% | Yes, see [5,6]. |
| Overall cost <$1 | No (>$1/test) | 51% | No, stand alone test. |
| Multiple analytes | No | 31% | Yes, Gal-1-P, Gal. |
| Secondary targets | No (lack of consensus) (*) | 49% | GALK and GALE are secondary targets of screening by galactose levels but not GALT activity [6]. |
| Multiplex platform | No | 19% | No. |
| The treatment | | | |
| Availability & cost | Widely available | 92% | Dietary management and monitoring require involvement of metabolic physician [1]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 73% | Cataracts may be reversible if a galactose-free diet is intiated in early infancy [2-4]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 70% | Cataracts may be reversible if dietary treatment is started in early infancy [2]. |
| Benefits of early identification | SOME benefits to family and society (lack of consensus) (*) | 69% | Genetic counseling is available [1]. |
| Prevention of mortality | No | 15% | Mortality is not a manifestation of this condition [2-4]. |
| Confirmation of diagnosis | Limited availability | 53% | Elevated galactose and normal GALT activity with reduced galactokinase activity are diagnostic [1]. RBC Gal-1-P and urinary galactitol are high. |
| Acute management | Widely available | 81% | Management of cataracts is widely available [1]. |
| Simplicity of therapy | Periodic involvement of specialist | 69% | Dietary management and monitoring require involvement of metabolic physician [1]. |

**Galactokinase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | 0 |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1286 /2100 | % of max score | 61% |
| Rank: | 0.69 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

GALK is not detected in screening if only GALT activity is measured. GALK deficiency is a secondary target of GALT screening.

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| | |
|---|---|
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| CONDITION | Galactose epimerase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of carbohydrate metabolism |
| ETHNICITY | Panethnic except generalized deficiency only seen in two Asian families. |
| SCREENING METHOD(S) | Microbiologic for G-1-P and galactose and fluorometric assays for GALT acitivity |
| NBS STATUS in the US | Screened for in 51 of 51 states, 100**%** of annual births (August 2004) |

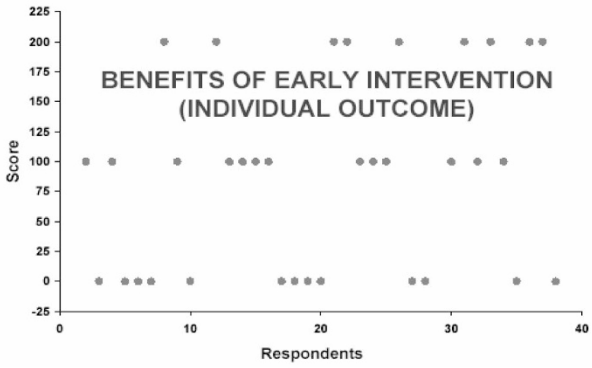
| Responses: | **38** | Valid scores: | 648 | 95% | PubMed references (August 2004) | 78 |
|---|---|---|---|---|---|---|

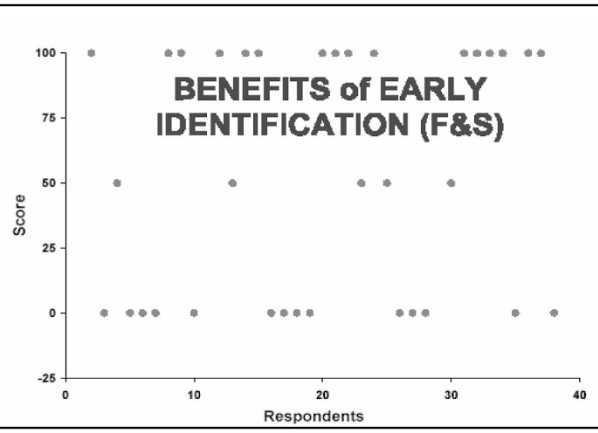
| Gene | *GALE* | Locus | *1p36-p35* | OMIM | *230350* |
|---|---|---|---|---|---|

| **SURVEY SCORES** | | % of max score | **LITERATURE AND WEB-BASED EVIDENCE** [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 7% | Incidence is unknown. Estimated as very rare at <1:100,000 with fewer than 10 families described [1]. |
| Phenotype at birth | Almost never | 84% | Usually asymptomatic, as there is not a severe enzyme deficiency in liver and probably other organs [1-4]. |
| Burden if untreated | Moderate | 41% | Most cases are asymptomatic. Liver disease and failure to thrive, as in GALT deficiency, in the extremely rare generalized deficiency form [1-4]. |
| The test | | | |
| Screening test | Yes | 75% | Beutler fluorescent spot screening test for GALT activity described in 1966 [5]. Gal-1-P and Gal levels are also screened by HPLC [6] in most states [7]. |
| Doable in DBS or by physical method | Yes | 83% | Yes, see [5,6]. |
| High throughput | Yes | 76% | Yes, see [5,6]. |
| Overall cost <$1 | No (>$1/test) | 50% | No, stand alone assays [5,6]. |
| Multiple analytes | No | 31% | No. |
| Secondary targets | No | 44% | No. |
| Multiplex platform | No | 18% | No. |
| The treatment | | | |
| Availability & cost | Widely available | 91% | Galactose free diet until further characterized and involvement of a metabolic disease physician. Treatment is generally not needed [2,3]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 40% | Symptomatology of extremely rare generalized form may be reduced [1-4]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome (lack of consensus) (*) | 44% | Most are asymptomatic but symptomatology of extremely rare generalized form may be reduced [1-4]. |
| Benefits of early identification | SOME benefits to family and society (lack of consensus) (*) | 53% | Genetic counseling available [2]. |
| Prevention of mortality | No | 17% | Mortality is not a significant component of phenotype [1]. |
| Confirmation of diagnosis | Limited availability | 40% | Elevated galactose-1-phosphate, reduced epimerase activity but normal GALT activity is diagnostic [1,2]. |
| Acute management | Widely available | 70% | Dietary management to remove galactose can prevent the life-threatening complications of classical galactosemia until patient is diagnosed [1-4]. |
| Simplicity of therapy | Periodic involvement of specialist | 62% | Metabolic specialists for dietary management and monitoring are of limited availability [2]. |

**Galactose epimerase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | 0 |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1066 | % of max score | 51% |
| Rank: | 0.35 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

GAL epimerase deficiency is confined to erythrocytes in most cases and affected individuals are asymptomatic. Generalized deficiency is very rare with only 5 cases reported as of 2001 but appears associated with developmental delay. However, consanguinity complicates determination of features solely associated with epimerase deficiency. GALE deficiency is a secondary target of GALT screening.

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| | |
|---|---|
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| 7 | NNSGRC data reported by programs [last updated April, 2004]. |

| CONDITION | Congenital disorder of glycosylation type Ib |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of glycosylation |
| ETHNICITY | Panethnic |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (as August 2004) |

| Responses: | 34 |
|---|---|

| Valid scores: | 570 | 93% |
|---|---|---|

| PubMed references (August 2004) | 373 |
|---|---|

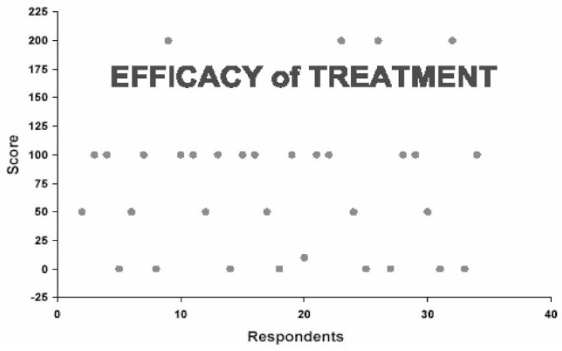
| Gene | *MPI* | Locus | *15q22-ter* | OMIM | *602579* |
|---|---|---|---|---|---|

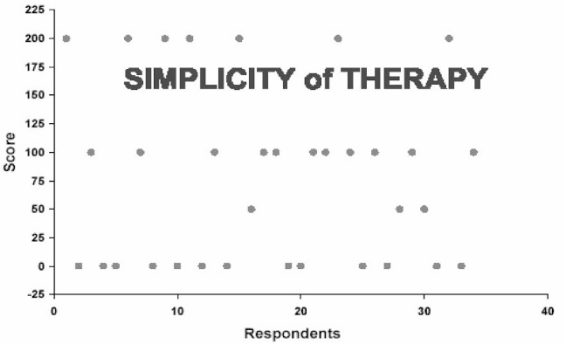
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 16% | Very rare but not known. <10 cases described though likely underdiagnosed [1-5]. |
| Phenotype at birth | <25% of cases | 66% | No dysmorphology as in type 1A. Patients present between 1 month and 1 year [1-5]. |
| Burden if untreated | Profound | 89% | Variable phentotype with hyperinsullinemic hypoglyemia, hypoalbuminemia, coagulopathy and potentially death if untreated. One adult with PMI deficiency and typical symptoms in infancy was healthy at 33 yrs. She was not treated with mannose [1-7]. |
| The test | | | |
| Screening test | No | 33% | No sensitive and specific screening test that is validated in a general population exists. A method for large scale automated screening of PMI and PMM activity has been described but has not been studied in clinical trials [8,9]. |
| Doable in DBS or by physical method | No | 33% | Not applicable. |
| High throughput | No | 11% | Not applicable. |
| Overall cost <$1 | No >$1/test) | 11% | Not applicable. |
| Multiple analytes | No | 10% | Not applicable. |
| Secondary targets | No | 19% | Not applicable. |
| Multiplex platform | No | 4% | Not applicable. |
| The treatment | | | |
| Availability & cost | Limited availability | 45% | Experienced metabolic disease physicians for oral mannose delivery and monitoring to treat gastrointestinal symptoms including protein-losing enteropathy, bleeding, hypoglycemia and hypoalbuminemia are of limited availability [2,4,9-11]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences (lack of consensus) (*) | 38% | Oral mannose resolves gastrointestinal bleeding and chronic diarrhea and improves mortality. Long-term administration of mannose was tolerated in control mice and in one patient for five years with continued benefit [2,4,6-8,12,15]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 44% | Resolution of gastrointestinal bleeding and chronic diarrhea improves quality of life and improves mortality [2,4,6,9,10,15]. |
| Benefits of early identification | SOME benefits to family and society | 63% | Genetic counseling and prenatal diagnosis [5,16]. |
| Prevention of mortality | No | 42% | Oral mannose improves mortality [2,4,6,9,10,15]. |
| Confirmation of diagnosis | Only a few centers | 28% | Isoelectric focusing of serum sialotransferrins and phosphomannose isomerase activity. Capillary electrophoresis and ESI tandem MS is replacing the original method for characterizing transferrin isoforms. Phosphomannosemutase activity of lymphoblasts and fibroblasts is available. Molecular diagnostics available [2,4,13,15,17]. |
| Acute management | Limited availability | 42% | Symptomatic treatment and oral mannose to manage chronic diarrhea, hypoglycemia and chronic diarrhea and improve mortality [2,4,9,10,15]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 39% | Metabolic disease physicians are of limited availability. |

**Congenital disorder of glycosylation type Ib**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**Congenital disorder of glycosylation type 1b**

**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No test |
| Final score | 766 /2100 | % of max score | 36% |
| Rank: | 0.11 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Congenital disorder of glycosylation type Ib lacks a validated test. Tests under development may perform better after two weeks of life than during the 24 - 48 hr. period after birth. Mannose therapy has only been available for 5 years so long-term effectiveness and/or adverse effects are still to be determined. Continued documentation of cases on mannose therapy is needed to extablish accurate therapeutic regimens.

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# PRIMARY IMMUNODEFICIENCIES

| CONDITION | Adenosine deaminase deficiency |
|---|---|
| TYPE of DISORDER | Genetic condition |
| ETHNICITY | Pan-ethnic |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

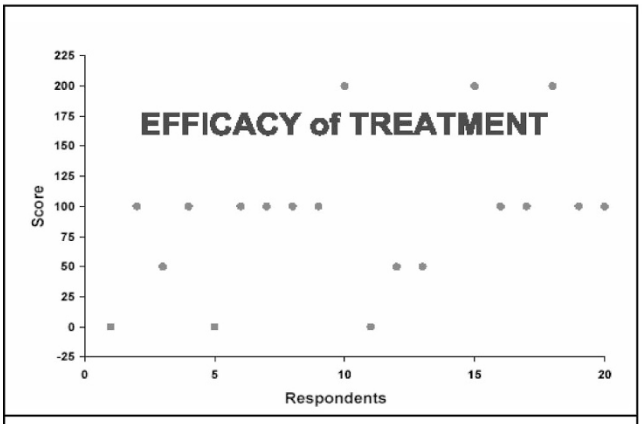
| Responses: | 20 | Valid scores: | 330 | 92% | PubMed references (August 2004) | 6,145 |
|---|---|---|---|---|---|---|

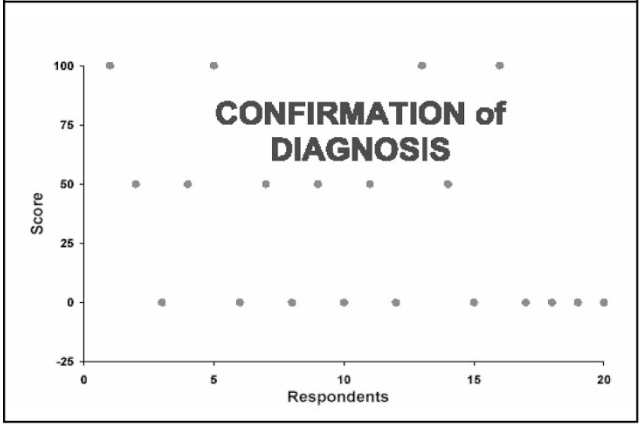
| Gene | *ADA* | Locus | *20q13.11* | OMIM | *102700* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | >1:75,000 | 21% | Unknown, estimated between 1:200,000 and 1:1,000,000 [1]. |
| Phenotype at birth | Almost never | 88% | All are normal at birth. Transplacentally transferred maternal IgG protects infants for first few weeks of life. SCID presents in the first weeks to few months of life with thrush, pneumonia and failure to thrive [2]. |
| Burden if untreated | Profound | 25% | For the 85 - 90% of cases with the more severe SCID presentation, it is usually fatal in the first year of life from opportunistic infections if not treated [3]. |
| The test | | | |
| Screening test | Yes | 60% | No test has been validated in a large general population in a public health setting. Enzyme activity can be measured from filter-paper blood spots [4,5]. T cell leukopenia should discriminate SCID patients [6]. A new PCR test for T cell circular DNA is being developed [1,4]. |
| Doable in DBS or by physical method | Yes | 61% | Yes [4,5]. |
| High throughput | No | 33% | Not applicable. |
| Overall cost <$1 | No (>$1/test) | 27% | Not applicable. |
| Multiple analytes | No | 13% | Not applicable. |
| Secondary targets | No | 0% | Not applicable. |
| Multiplex platform | No | 0% | Not applicable. |
| The treatment | | | |
| Availability & cost | Not available | 24% | Regional centers for bone marrow transplant are available; subsequent follow-up is widely available. Bone marrow transplant prior to infection complications on the order of $40,000; subsequently patient may be cured or may need IVIG monthly for some years [7,8] Enzyme replacement with PEG-modified ADA provided clinical and immunologic improvement in 100 patients [9,10,11]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (lack of consensus) (*) | 46% | Up to 95% survival; around 50% are completely cured [7,13,15]. Enzyme replacement with PEG-modified ADA provided clinical and immunologic improvement in 100 patients [9,10,11]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 50% | Survival and better immune restoration [12,13]. Transplant cost would about $40,000 if done early vs. cost for care of infections plus transplant of about $1,000,000 after symptoms. [14]. |
| Benefits of early identification | SOME benefits to family and society | 58% | Genetic counseling and prenatal diagnosis are available [16,17]. DNA testing is available [6,18,19]. |
| Prevention of mortality | Yes | 74% | Yes. T cell depleted bone marrow transplantation is preferred treatment but is of limited availability and high cost [7,8]. Enzyme replacement with PEG-modified ADA provided clinical and immunologic improvement in 100 patients [9,10,11]. |
| Confirmation of diagnosis | Only a few centers (lack of consensus) (*) | 35% | ADA activity to show very low to absent activity is available through reference laboratories. Over 50 mutations have been described in the ADA gene but enzyme testing is adequate [6,18,19]. |
| Acute management | Only in a few centers | 26% | Bone marrow transplantation, either from HLA-matched sibling, half-matched parent or matched unrelated donor with cost of care for infections reaching $1,000,000 or more [14,20]. |
| Simplicity of therapy | Regular involvement of specialist | 11% | Initial treatment, BMT, complex; follow-up by pediatric immunologists. Similarly, enzyme replacement therapy is complex and of very limited availability [7-11]. |

## Adenosine deaminase deficiency

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




### INCLUSION CRITERIA

| | | | |
|---|---|---|---|
| Test available | Yes | Type | 0 |
| 2ary target of higher scoring condition? | | | No |
| Final score | 841 /2100 | % of max score | 40% |
| Rank: | 0.18 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

### ASSESSMENT

**Not included in uniform panel (test available)**

### COMMENT

85 - 90% of cases present with the more severe form, SCID. The balance present later with a combined immunodefiency syndrome. New York State screened for ADA deficiency by an enzyme activity assay for several years in the 1970s. The program was dropped when no cases were found among 2.56 million newborns. Hence, pilot studies to determine actual prevalence are needed. There were differences between the literature and the surveys in that a test is available. It is on the basis of its rarity that screening has not proceeded. However, it would be detected if a global SCID test was used [see SCID].

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| CONDITION | Severe combined immunodeficiency (SCID) |
|---|---|
| TYPE of DISORDER | Genetic condition, at least 9 different types |
| ETHNICITY | No known ethnic differences |
| SCREENING METHOD(S) | No test available at the present time |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | 69 | Valid scores: | 1,187 | 96% | PubMed references (August 2004) | 3,106 |
|---|---|---|---|---|---|---|

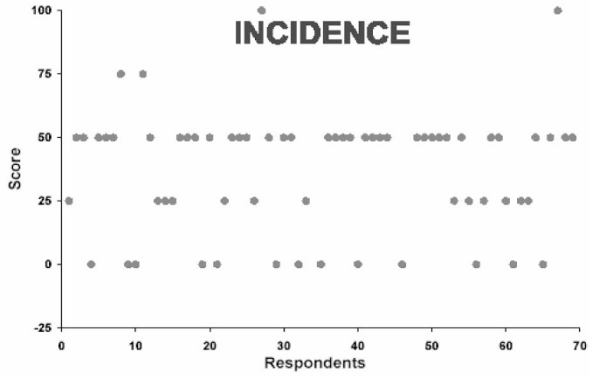
| Gene | *SCID1* | Locus | *8q11* | OMIM | *202500 & others* |
|---|---|---|---|---|---|

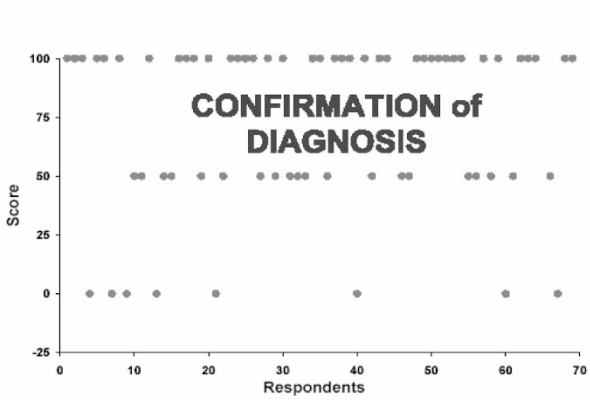
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 38% | Unknown; estimates of 1:100,000 are low, missing undiagnosed affected infants who die of infections [1]. |
| Phenotype at birth | Almost never | 86% | Patients are asymptomatic at birth. Transplacentally transferred maternal IgG protects infants for first few weeks of life. [2] SCID presents in the first year of life [3]. |
| Burden if untreated | Profound | 98% | Thrush, diarrhea, failure to thrive; infections with bacteria, fungi, viruses, and generally fatal in first weeks of life [3]. |
| The test | | | |
| Screening test | Yes | 67% | No. T cell leukopenia should discriminate SCID patients [6]. A new PCR test for T cell circular DNA is being developed [1,4]. No test has been validated in a large general population in a public health setting. |
| Doable in DBS or by physical method | Yes | 55% | Not available evidence at the present time. |
| High throughput | No | 9% | Not available evidence at the present time. |
| Overall cost <$1 | No (>$1/test) | 5% | Not available evidence at the present time. |
| Multiple analytes | No | 6% | No. |
| Secondary targets | No | 0% | No. |
| Multiplex platform | No | 0% | No. |
| The treatment | | | |
| Availability & cost | Limited availability | 38% | Regional centers for bone marrow transplant are available; subsequent follow-up widely available. Bone marrow transplant prior to infection complications on the order of $100,000; subsequently patient may be cured or may need IVIG monthly for some years [3]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 51% | Up to 95% survival; around 50% are completely cured, with others requiring IVIG [3,5,6,7]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 86% | Survival and better immune restoration [3,5,6,7]. Transplant cost would be $40,000 if done early vs. cost care for infections and transplant of about $1,000,000 after symptoms. |
| Benefits of early identification | CLEAR benefits to family and society | 89% | Genetic counseling, carrier detection and prenatal diagnosis available [8,9,10,11]. |
| Prevention of mortality | Yes | 93% | Yes [5]. |
| Confirmation of diagnosis | Widely available (lack of consensus) (*) | 73% | Cell surface markers to enumerate T and B cells widely available; pediatric immunology centers needed for specific phenotype and genotype determination [10]. |
| Acute management | Limited availability | 44% | Bone marrow transplantation, either from HLA-matched sibling, half-matched parent or matched unrelated donor [11]. |
| Simplicity of therapy | Regular involvement of specialist | 9% | Initial treatment, BMT, complex; follow-up by pediatric immunologists. IVIG can be admistered at home with immunologist guidance; self administered subcutaneous immunoglobulin is gaining favor in US, already widely used in Europe [10,12]. |

**Severe combined immunodeficiency (SCID)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1047 /2100 | % of max score | 50% |
| Rank: | 0.33 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

SCID includes 9 conditions (IL-7Ra, CD45, JAK3, RAG1, RAG2, Artemis, ADA deficiency and XL-SCID) [9]. New methodologies are in trials for screening by way of PCR test for T cell circular DNA but this test is not yet validated in a general population. Significant discrepancies between literature and surveys involved availability of a test.

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| | |
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# OTHER GENETIC AND NON-GENETIC CONDITIONS

| CONDITION | Alpha-1-Antitrypsin deficiency |
|---|---|
| TYPE of DISORDER | Genetic condition |
| ETHNICITY | Found predominantly in Caucasians. |
| SCREENING METHOD(S) | Isoelectric focusing; fluorometric enzyme inhibition assays |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

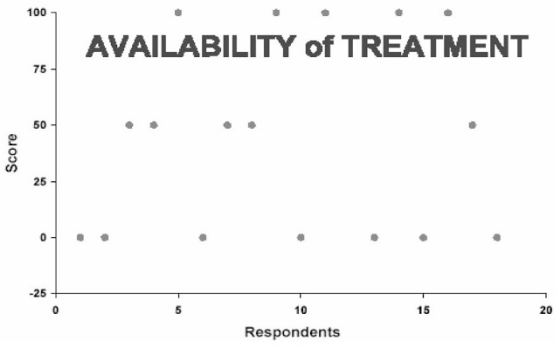
| Responses: | 18 | Valid scores: | 285 | 88% | PubMed references (August 2004) | 9,770 |
|---|---|---|---|---|---|---|

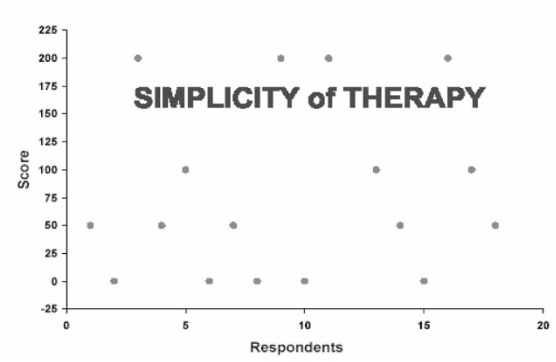
| Gene | *PI* | Locus | *14q32.1* | OMIM | *107400* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:25,000 | 74% | PI ZZ genotype is 1/7000 Caucasians; 1/3,000 Scandinavians. Studies in the US showed a prevalence of 1/2,857 - 1/5,0097. Rare in Blacks and Asians. The PI S allele is also associated with A1AT deficiency. (Not a disease incidence) [1-3]. |
| Phenotype at birth | Almost never | 83% | Jaundice is only rarely appreciated in neonates (though 10% may have it) with PI ZZ genotype. Liver or lung disease have later onset [4-9]. |
| Burden if untreated | Moderate | 54% | Highly variable. About 17% of infants with PI ZZ will show clinically recognizable abnormalities of liver function. About 10% of these may have a poor prognosis. Major risk is for later onset obstructive lung disease [4-9]. Small risk of hepatoma [4,5]. |
| The test | | | |
| Screening test | Yes | 61% | Isoelectric focusing and silver staining was used in Sweden [10-12]. |
| Doable in DBS or by physical method | Yes | 59% | Yes, see [1,10]. |
| High throughput | No | 29% | Yes, see [1-3]. |
| Overall cost <$1 | No (>$1/test) | 23% | No, stand-alone assay. |
| Multiple analytes | No | 0% | Yes, multiple PI variants are detected [12]. |
| Secondary targets | No | 0% | No. |
| Multiplex platform | No | 0% | No. |
| The treatment | | | |
| Availability & cost | Limited availability (lack of consensus) (*) | 44% | The "treatment" in response to screening positively for PI ZZ is avoidance of smoking by children [10]. The liver disease seen in 2-3% of cases cannot be prevented. However, liver transplantation for severe disease is available. A1AT augmentation therapy is of limited availability [4,5,18,20]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 25% | Avoidance of smoking significantly delays the onset of chronic obstructive lung disease [1,6,18]. |
| Benefits of early intervention | NO evidence that early intervention optimizes individual outcome | 15% | Avoidance of smoking significantly delays the onset of chronic obstructive lung disease [1,7,16]. |
| Benefits of early identification | SOME benefits to family and society | 44% | Genetic counseling and prenatal diagnosis are available [4,7]. |
| Prevention of mortality | No | 7% | About 2.5% of individuals with A1AT deficiency die of cirrhosis by age 18 yrs. Preventive measures related to chronic obstructive pulmonary disease lengthen life span [3,9]. |
| Confirmation of diagnosis | Widely available | 85% | PI typing by isoelectric focusing and molecular diagnostics [10]. |
| Acute management | Limited availability | 62% | The range of liver and pulmonary disease in individuals with Pi ZZ requires multiple specialists and may be restricted to centers. Liver and lung transplant for severe cases. Human α1AT therapy in some clinically affected cases [1,3,11,13]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 40% | The range of liver and pulmonary disease in individuals with PI ZZ requires multiple specialists and may be restricted to centers where transplantation and specialized therapies are available [3]. |

## Alpha-1-Antitrypsin deficiency

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | 0 |
| 2ary target of higher scoring condition? | | | No |
| Final score | 819 /2100 | % of max score | 39% |
| Rank: | 0.16 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

**ASSESSMENT**

**Not included in uniform panel (test available)**

**COMMENT**

α1AT screening is used to identify a susceptibility to liver and lung disease. The Swedish program highlighted the potential for negative psychological side effects in screening for conditions for which many identified individuals will not develop disease for which no therapy is available, except for transplantation [19]. Surveys indicated that screening tests were of limited availability (which is true in the US due to choices not to screen) and were not high-throughput. However, experience in Sweden indicates that newborn screening is feasible [19]. The Consensus Statement of the American Thoracic Society and the European Respiratory Society recommends against newborn screening outside of countries with prevalence >1/1,500, high prevalence of smoking and adequate counseling services available.

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| | |
|---|---|
| **CONDITION** | **Biliary atresia** |
| TYPE of DISORDER | May be final common endpoint for a variety of infectious, genetic or congenital disorders |
| ETHNICITY | Panethnic |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | 15 | Valid scores: | 237 | 88% |
|---|---|---|---|---|

| PubMed references (August 2004) | 2,266 |
|---|---|

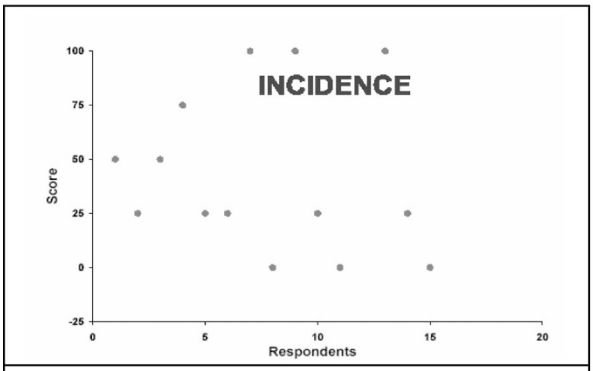
| Gene | *EHBA* | Locus | *unknown* | OMIM | *210500* |
|---|---|---|---|---|---|

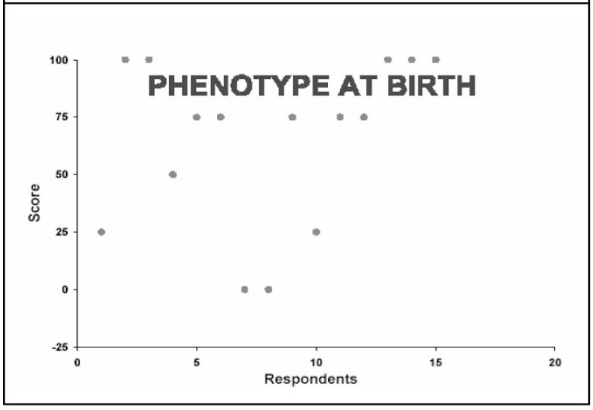
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:50,000 (lack of consensus) (*) | 43% | 1:500 - 2,500 have hyperbilirubinemia due to cholestatic hepatobiliary disease and 1:10,000 - 20,000 due to extrahepatic biliary atresia. About 1:8,000 in total [1,2,3]. |
| Phenotype at birth | <25% of cases (lack of consensus) (*) | 65% | Jaundice is very common in neonates with 2.4 - 15% remaining jaundiced beyond 14 days [4,5]. |
| Burden if untreated | Profound | 93% | Life threatening bleeding or brain damage from vitamin K malabsorption [6]. Most all would die of complications of biliary atresia without surgery (portoenterostomy) or liver transplant [11]. |
| The test | | | |
| Screening test | No | 15% | No general-population vaildated screening test for bilirubin is available[7,8]. MS/MS for bile acids at three weeks of life had inadequate sensitivity [9]. |
| Doable in DBS or by physical method | No | 17% | Not applicable. |
| High throughput | No | 0% | Not applicable. |
| Overall cost <$1 | No (>$1/test) | 9% | Not applicable. |
| Multiple analytes | No | 0% | Not applicable. |
| Secondary targets | No | 10% | If screened by bilirubin, there would be many potential etiologies. |
| Multiplex platform | No | 10% | Not applicable. |
| The treatment | | | |
| Availability & cost | Not available | 27% | Surgery for biliary atresia prior to 60 days of life is widely available and includes 'Centers of Excellence.' Liver transplants are widely available, though limited by cost and access [10-14]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 34% | Surgery prior to 60 days resolves jaundice in 50-75% of cases, 87% of which have 15+ yrs. survival. Most ultimately need transplant due to progressive biliary cirrhosis even if biliary drainage is established [10-14]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 50% | When portoenterostomy is done prior to 60 days of life while native liver is still present, survival is significantly improved. Most patients experince medical problems after surgery [10-16]. |
| Benefits of early identification | SOME benefits to family and society | 63% | Bilirubin screening would identify disorders with biliary atresia and other heritable conditions (e.g., α-1-antitrypsin deficiency, G6PD deficiency, Allagille syndrome) that would inform family members of risks [2,14]. |
| Prevention of mortality | Yes | 71% | Surgery prior to 60 days resolves jaundice in 50-75% of cases. 80 - 90% of which have 15+ yrs. survival versus death by age 1 [10,12-14]. |
| Confirmation of diagnosis | Limited availability | 79% | There is an extensive differential diagnosis depending on ascertainment. Some diagnostic procedures and tests are less widely available [11-14]. |
| Acute management | Limited availability | 44% | Surgery for biliary atresia is of moderately limited availability [11-14]. |
| Simplicity of therapy | Regular involvement of specialist | 7% | Involvement of specialist, particularly following liver transplant is needed [11-14]. |

**Biliary atresia**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No test |
| Final score | 744 /2100 | % of max score | 35% |
| Rank: | 0.08 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Experts consulted on hyperbilirubinemia considered that change in practice to monitor bilirubin in all newborns in the nursery was needed. Some etiologies of hyperbilirubinemia require prompt response that may be better managed locally. A stool color card screening test at age one month is being tested in Taiwan and Japan.

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| CONDITION | Biotinidase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error of metabolism |
| ETHNICITY | Highest incidence in Caucasians |
| SCREENING METHOD(S) | Colorimetric assay (inconsistently detected by MS/MS) |
| NBS STATUS in the US | Screened for in 31 of 51 states, 52% of annual births (August 2004) |

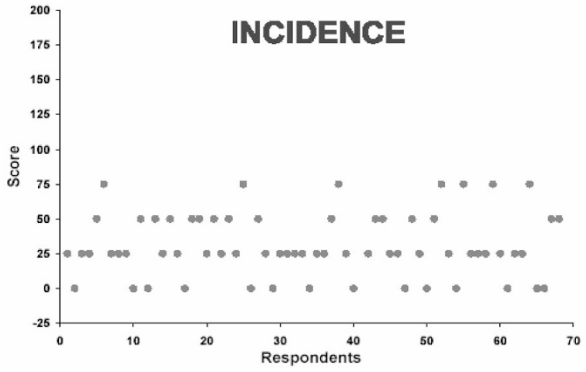
| Responses: | 68 | Valid scores: | 1,198 | 98% | PubMed references (August 2004): | 349 |
|---|---|---|---|---|---|---|

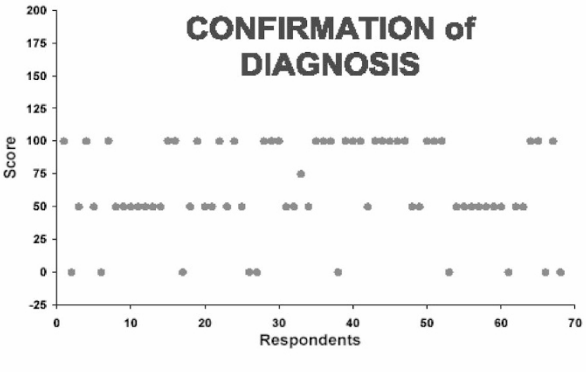
| Gene | *BTD* | Locus | *3p25* | OMIM | *253260* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 31% | 1:61,319 in US newborn screens of 12,754,403 newborns [1]. Profound (<10%) and partial (10-30%) defects of serum activity have been described in nearly equal proportions [2]. |
| Phenotype at birth | Almost never | 96% | Presentation is usually between 3 and 6 months. Non-penetrant cases have been described [2,3]. |
| Burden if untreated | Profound | 84% | Developmental delay, hypotonia, hearing loss, optic atrophy myoclonic seizures, skin rash, alopecia, ataxia and death [3,4,12,14]. |
| The test | | | |
| Screening test | Yes | 98% | Semi-quantitative or qualitative colorimetric assay [3,5,7]. |
| Doable in DBS or by physical method | Yes | 99% | Yes [5]. |
| High throughput | Yes | 86% | Up to 500-1,000 specimens per day [5,6,7]. |
| Overall cost <$1 | <$1/test | 66% | Ranges from $0.30 - $1.00 [8]. |
| Multiple analytes | No | 20% | No. |
| Secondary targets | No | 19% | No. Cases with holocarboxylase synthetase deficiency (MCD) have normal biotinidase activity [11]. |
| Multiplex platform | No | 19% | No. Anecdotal reports of cases detected by MS/MS acylcarnitine profiling. |
| The treatment | | | |
| Availability & cost | Widely available | 99% | Biotin treatment is widely available and inexpensive ($100 - $300 per year) [8]. |
| Efficacy of treatment | Potential to prevent ALL negative consequences | 85% | Rapid and usually complete regression of symptoms. Hearing loss and optic atrophy are less reversible [9,10,11,12]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcomes | 88% | Complete prevention of clinical manifestations [9,10,11,12]. |
| Benefits of early identification | CLEAR benefits to family & society | 92% | Identification of other at-risk family members; genetic counseling and prenatal diagnosis are available [9]. |
| Prevention of mortality | Yes | 82% | Acute episodes of metabolic decompensation are life-threatening events [9,10]. |
| Confirmation of diagnosis | Limited availability (lack of consensus) (*) | 64% | Serum biotinidase assay, urine organic acids (3-OH isovaleric acid), plasma and urine acylcarnitines (C5-OH). Stability and heat-sensitivity of biotinidase activity could be an issue. |
| Acute management | Widely available | 80% | Rapid regression of symptoms with biotin treatment [3,13]. |
| Simplicity of therapy | Primary care, family level | 82% | 5-20 mg/day of biotin po [3]. |

**Biotinidase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | Colorimetric |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1566 /2100 | % of max score | 75% |
| Rank: | 0.95 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Biotinidase deficiency had one the highest scores of the panel of conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel.

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| CONDITION | Cystic fibrosis |
|---|---|
| TYPE of DISORDER | Genetic condition |
| ETHNICITY | Occurs predominantly in Caucasians of Western European ancestry and seems to be less common in African Americans and Hispanics; rare in Asians and Asian-Americans. |
| SCREENING METHOD(S) | Immunoreactive trypsinogen (IRT) plus 2nd tier DNA |
| NBS STATUS in the US | Screened for in 3 of 51 states, 7% of annual births (August 2004) |

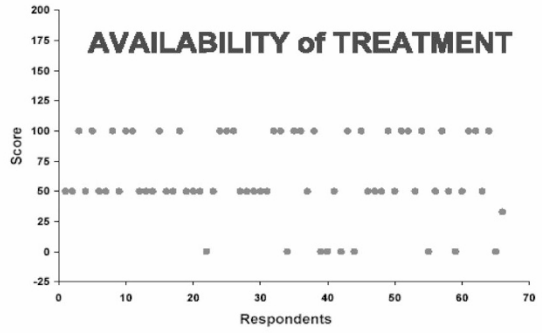
| Responses: | 65 | Valid scores: | 1,086 | 96% | PubMed references (August 2004): | 23,628 |
|---|---|---|---|---|---|---|

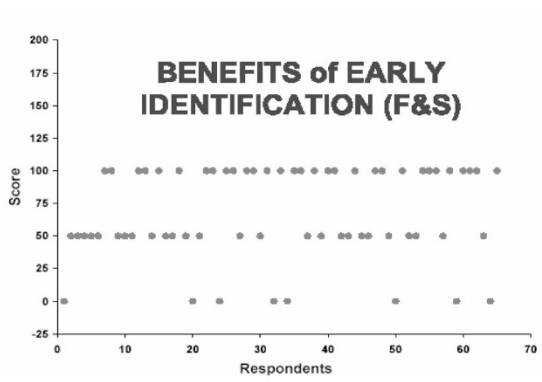
| Gene | *CFTR* | Locus | *CFTR* | OMIM | *219700* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | 3 | |
| The condition | | | | |
| Incidence | >1:5,000 | 95% | | CF occurs in 1:3,721 in 1,459,834 screened US newborns [2]. 1:2,500 Caucasians, 1:8,000 Hispanics, 1:15,300 African Americans, 1:32,000 Asian Americans [1,3,4]. |
| Phenotype at birth | <25% of cases | 76% | | Fetuses and newborns with meconium ileus may be detected prior to or at birth [5]. |
| Burden if untreated | Profound | 84% | | Late diagnosis is associated with more severe pulmonary disease [6, 7]. |
| The test | | | | |
| Screening test | Yes | 92% | | The screening test algorithm involves IRT followed by IRT or DNA (mutation distribution varies) testing [8]. |
| Doable in DBS or by physical method | Yes | 90% | | IRT/DNA done in dried blood spots [9]. |
| High throughput | Yes | 68% | | IRT is high throughput; DNA testing is moderate throughput [10]. |
| Overall cost <$1 | No | 38% | | Wide variability in costs per birth [10]. |
| Multiple analytes | No | 25% | | No. |
| Secondary targets | No | 23% | | No. |
| Multiplex platform | No | 24% | | Not for IRT; second tier multiplex DNA testing is available. |
| The treatment | | | | |
| Availability & cost | Limited availability (lack of consensus) (*) | 67% | | Improved nutritional support [11]. Most CF centers are at academic medical centers so they are of moderate availability. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 32% | | Early identification improves growth over the short term and reduces infections. Morbidity reduction increases lifespan. Mortality is reduced in early childhood [11]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome (lack of consensus) (*) | 50% | | Interventions ameliorate and/or delay onset of some features [10]. |
| Benefits of early identification | SOME benefits to family and society | 72% | | Genetic counseling, molecular testing and prenatal diagnosis are available [3]. |
| Prevention of mortality | No | 31% | | Mortality delayed, but not normal. Benefit apparent in some studies (Wales) but not in others (Australia) suggesting reduced mortality in infants in screened populations [13]. |
| Confirmation of diagnosis | Widely available | 88% | | Sweat testing is widely available and DNA testing is readily accessible [10]. |
| Acute management | Limited availability | 72% | | Pulmonology and infectious disease management widely available. CF Centers are distributed nationally [3]. |
| Simplicity of therapy | Regular involvement of specialist | 26% | | Varies with symptoms [3]. |

**Cystic fibrosis**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | YES | Type | IRT/DNA |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1200 /2100 | % of max score | 57% |
| Rank: | 57 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Cystic fibrosis screening is supported by a growing body of evidence. Nutritional benefits shown by improved growth were less pronounced after 5 years than they appeared in the first 1 - 2 years but do persist for many years. However, recent evidence suggests that nutritional benefits may have a positive influence on cognitive abilities and also have a positive influence by improving pulmonary function, though the data was not published at the time we ceased collections (February, 2004). CF screening should be reevaluated based on this evidence that is expected to improve its rating.

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| | |
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| CONDITION | **Duchenne (DMD) and Becker (BMD) muscular dystrophy** |
|---|---|
| TYPE of DISORDER | Genetic condition |
| ETHNICITY | Panethnic |
| SCREENING METHOD(S) | Creatine kinase by fluorescent spot assays where screening is done |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | **20** | Valid scores: | 491 | 92% |
|---|---|---|---|---|

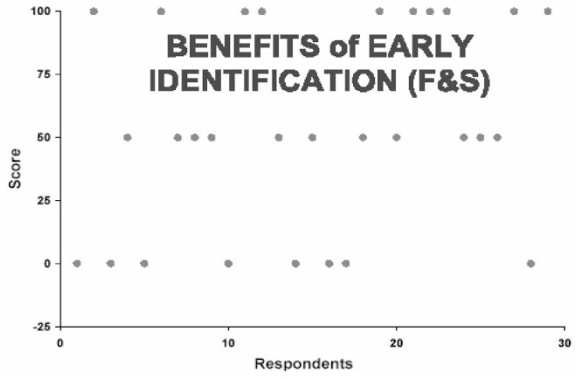
| PubMed references (August 2004) | 5184 |
|---|---|

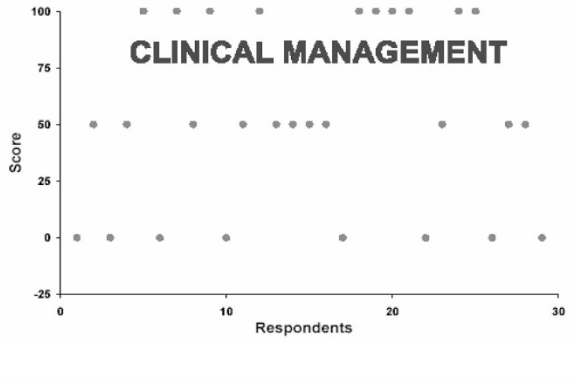
| Gene | *DMD BMD* | Locus | *Xp21.2 12q21* | OMIM | *310200; 300376* |
|---|---|---|---|---|---|

| **SURVEY SCORES** | | % of max score | **LITERATURE AND WEB-BASED EVIDENCE** [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | >1:25,000 | 71% | Birth incidence in northern England of DMD is 1:5,618 males and of BMD is 1:18,540 [1], 1:3,000 overall [2]. |
| Phenotype at birth | Almost never | 93% | DMD usually presents in early childhood [2,3]. |
| Burden if untreated | Profound | 83% | DMD progresses rapidly to being wheelchair bound by 12 yrs., cardiomyopathy in late teens and death in third decade. BMD progresses more slowly to a mean age of death in the 40s [3,4]. |
| The test | | | |
| Screening test | Yes | 52% | Creatine kinase is used in countries that screen [5]. |
| Doable in DBS or by physical method | Yes | 62% | Yes, see [5]. |
| High throughput | No | 52% | No. |
| Overall cost <$1 | No (>$1/test) | 30% | No, stand-alone assay. |
| Multiple analytes | No | 4% | No. |
| Secondary targets | No | 22% | No. |
| Multiplex platform | No | 9% | No. |
| The treatment | | | |
| Availability & cost | Not available | 30% | No definitive treatment currently exists for DMD and BMD [4,8,12]. |
| Efficacy of treatment | Treatment efficacy not proven | 10% | No definitive treatment currently exists for DMD and BMD [4,8,12]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 14% | No definitive treatment currently exists for DMD and BMD. Management can improve quality of life and can prolong life [4,8,12]. |
| Benefits of early identification | SOME benefits to family and society (lack of consensus) (*) | 53% | Genetic counseling and prenatal diagnosis are available [4,6-10]. |
| Prevention of mortality | Not available | 4% | Survival can be prolonged but treatment is not curative [4]. |
| Confirmation of diagnosis | Limited availability | 73% | Clinical features [4,11] and molecular diagnostics [6,7]. |
| Acute management | Limited availability (lack of consensus) (*) | 53% | Neuromuscular and neurogenetic physicans are not readily available [4]. |
| Simplicity of therapy | Regular involvement of specialist | 15% | Neuromuscular and neurogenetic physicans are not readily available. Specialist involvement is ongoing [4]. |

**Duchenne (DMD) and Becker (BMD) muscular dystrophy**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | 0 |
| 2ary target of higher scoring condition? | | | No |
| Final score | 776 /2100 | % of max score | 37% |
| Rank: | 0.12 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (test available)**

**COMMENT**

Lack of benefits of treatment contributed most to the low score for screening. Innovative therapies are in clinical trials [13].

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| | |
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| CONDITION | Familial hypercholesterolemia (heterozygote) |
|---|---|
| TYPE of DISORDER | Genetic Condition |
| ETHNICITY | Panethnic but higher in French Canadians in Quebec, Afrikaners and Lebanese. |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | 25 | Valid scores: | 393 | 87% | PubMed references (August 2004) | 4849 |
|---|---|---|---|---|---|---|

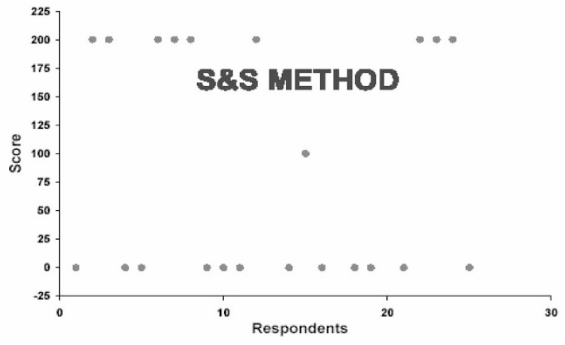
| Gene | *FHC LDLR* | Locus | *19p13.2; 1q21-q23; 9q22-* | OMIM | *143890* |
|---|---|---|---|---|---|

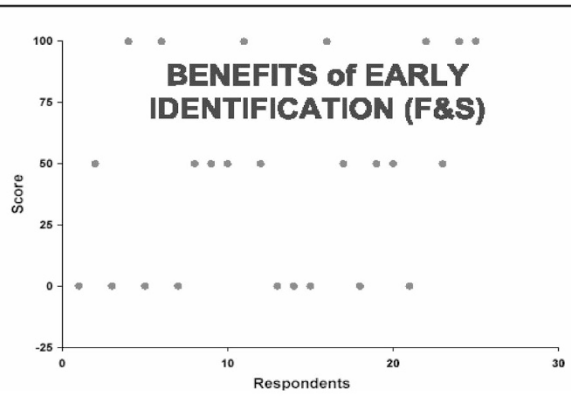
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:5,000 | 90% | Heterozygotes are 1:500; homozygotes are 1:1,000,000 [1,2]. |
| Phenotype at birth | Almost never | 96% | Heterozygotes have cholesterol levels of 350 - 550 mg/dl but little other phenotype during the first decade [2,3]. |
| Burden if untreated | Moderate | 53% | Tendon xanthomas in 2nd decade and coronary heart disease in 4th decade [4]. |
| The test | | | |
| Screening test | No | 43% | No sensitive and specific test that is validated in a general population exists. Blood spot assays have been described [5,6]. Specificity is poor [7]. |
| Doable in DBS or by physical method | No | 29% | Assays not validated in general populations [7]. |
| High throughput | No | 33% | Assays not validated in general populations [7]. |
| Overall cost <$1 | No (>$1/test) | 22% | Assays not validated in general populations [7]. |
| Multiple analytes | No | 17% | Assays not validated in general populations [7]. |
| Secondary targets | No | 29% | Assays not validated in general populations [7]. |
| Multiplex platform | No | 19% | Assays not validated in general populations [7]. |
| The treatment | | | |
| Availability & cost | Widely available | 86% | Low-saturated fat and low cholesterol diets. Statins can lower cholesterol levels by 10 - 20% and are widely available [8]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 34% | Statins can lower cholesterol levels by 10 - 20% and are widely available [8]. Pravastatin induces regression of carotid atherosclerosis in children with FH with no adverse effects on growth, sexual maturation or hormone levels. Slowing of progression of coronary atherosclerosis [9]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 30% | Statins slow the progression of coronary atherosclerosis [8,9]. |
| Benefits of early identification | SOME benefits to family and society | 46% | Genetic counseling and prenatal diagnosis available. Identification of other at-risk family members [10]. |
| Prevention of mortality | Yes | 58% | Slowing of progression of coronary atherosclerosis prolongs life [9]. |
| Confirmation of diagnosis | Widely available | 84% | Elevated plasma LDL usually shown by elevated cholesterol without hypertriglyceridemia is widely available. LDL receptor function tests less widely available [1,2,11]. |
| Acute management | Widely available | 88% | Cholesterol lowering statins are widely available. HMG CoA reductase available. LDL apheresis for homozygotes is available [2,10]. |
| Simplicity of therapy | Periodic involvement of specialist | 52% | Dietary management and monitoring require periodic involvement of specialists [2]. |

**Familial hypercholesterolemia (heterozygote)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1038 /2100 | % of max score | 49% |
| Rank: | 0.3 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

A screening test for familial hypercholesterolemia heterozygosity has not been validated in large general US population. It is clear that the elevated LDL associated with this disorder results in development and significant progression of atherosclerosis at an early age. Treatment can prolong life for many years. Studies of cholesterol and apolipoprotein B testing in newborn dried blood spots or at times early in childhood is required.

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| CONDITION | Fragile X syndrome |
|---|---|
| TYPE of DISORDER | Genetic condition |
| ETHNICITY | Panethnic [1]. |
| SCREENING METHOD(S) | No test available at present time |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

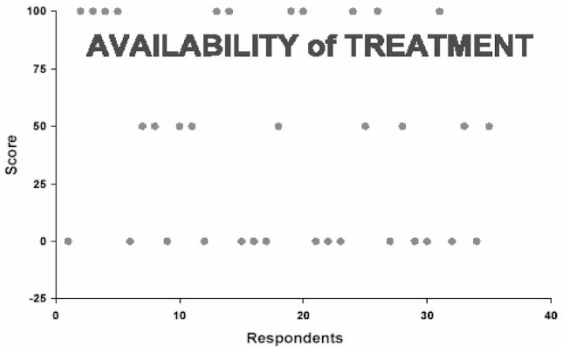
| Responses: | 35 | Valid scores: | 613 | 97% | PubMed references (August 2004) | 3356 |
|---|---|---|---|---|---|---|

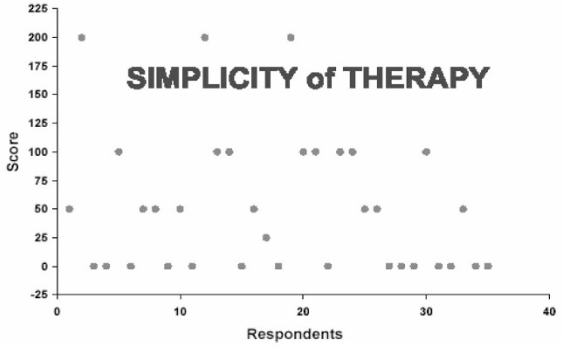
| Gene | *FMR1* | Locus | *Xq27.3* | OMIM | *309550* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:5,000 | 88% | 1:4,000 males; 1:8,000 females [2]. |
| Phenotype at birth | Almost never | 90% | Non-specific and often subtle phenotype in newborns [3]. |
| Burden if untreated | Severe | 73% | Moderate-severe mental retardation with behavioral abnormalities in males [4]. Average IQs of 75-90 in full mutation females [5,6]. |
| The test | | | |
| Screening test | No | 36% | No test has been validated in a large general population in a public health setting. No screening test available for FMR1 repeat expansions. |
| Doable in DBS or by physical method | No | 36% | No. |
| High throughput | Yes | 16% | No. |
| Overall cost <$1 | No (>$1/test) | 0% | Not applicable. |
| Multiple analytes | No | 3% | Not applicable. |
| Secondary targets | No | 3% | No. |
| Multiplex platform | No | 6% | Not applicable. |
| The treatment | | | |
| Availability & cost | Limited availability (lack of consensus) (*) | 44% | Symptomatic interventions to maximize vision and hearing, speech and language therapy, early learning intervention [6-8]. |
| Efficacy of treatment | Treatment efficacy not proven | 12% | Symptomatic interventions are proven. Early intervention should optimize but not normalize long-term cognitive outcome [9]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 26% | Early intervention can improve intellectual function, behavioral techniques assist with some behavioral problems [7]. |
| Benefits of early identification | SOME benefits to family and society | 71% | Average age of diagnosis is 30-34 months. Early identification allows for family planning [10]. |
| Prevention of mortality | No | 6% | Life expectancy is not markedly reduced in fragile X syndrome [6,7]. |
| Confirmation of diagnosis | Widely available | 81% | Molecular testing for FMR1 repeat amplification is widely available [11]. |
| Acute management | Limited availability | 63% | Symptomatic treatment of seizures, otitis media, etc. is generally available though coordination of care by an experienced professional is useful [6,7]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 26% | Multidisciplinary care is required [6,12]. |

**Fragile X syndrome**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No test |
| Final score | 776 /2100 | % of max score | 37% |
| Rank: | 0.12 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

There is no screening test available currently. Survey respondents indicated two areas of benefit from identification. Early intervention programs can improve intellectual outcome, though not normalize outcome. There was value placed on the knowledge of the disorder in an offspring to the family that was able to consider this in reproductive planning since most families have completed child-bearing by the time the first diagnosis of fragile X syndrome in an offspring is made.

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| CONDITION | Hearing loss |
|---|---|
| TYPE of DISORDER | Multiple types (syndromal 15%) |
| ETHNICITY | Ethnic differences in incidence and mutation distribution of specific genetic forms. |
| SCREENING METHOD(S) | Audiometry (TEOAE, BAER, OAE) |
| NBS STATUS in the US | Screened for in 42 of 51 states, 88% of annual births (August 2004) |

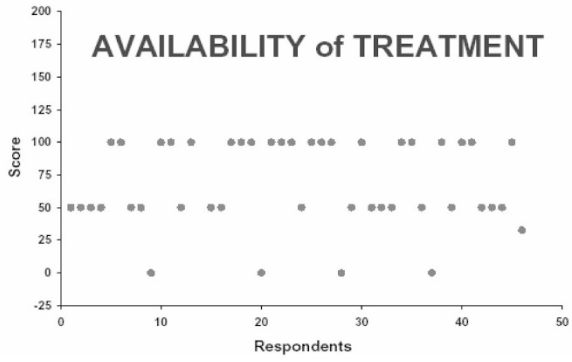
| Responses: | 42 | Valid scores: | 740 | 98% | PubMed references (August 2004): | 1,854 |
|---|---|---|---|---|---|---|

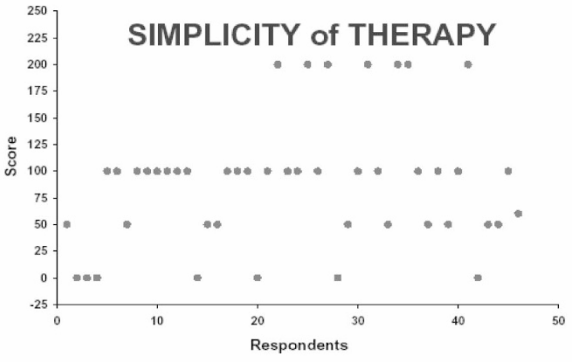
| Gene | *Many* | Locus | *Many* | OMIM | *Many* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| Criteria | Consensus | | |
| The condition | | | |
| Incidence | >1:5000 | 95% | Profound hearing loss occurs in 1:1,000 US newborns [1, 2, 3]. |
| Phenotype at birth | Almost never | 83% | May not be apparent in neonates with non-syndromal forms (85%) [1,4]. |
| Burden if untreated | Severe | 74% | Severe hearing loss [3, 5]. |
| The test | | | |
| Screening test | Yes | 89% | First available in mid-1960s [3, 6, 7]. |
| Doable in DBS or by physical method | Yes (Audiometry) | 80% | See [6, 7]. |
| High throughput | No | 13% | Test is functional and done on each newborn [3]. |
| Overall cost <$1 | No | 10% | $10 - $24 per newborn varying by test format chosen [8]. |
| Multiple analytes | No | 3% | No. |
| Secondary targets | No | 16% | May detects many etiologic forms of hearing loss [9]. |
| Multiplex platform | No | 3% | No. |
| The treatment | | | |
| Availability & cost | Limited availability (lack of consensus) (*) | 70% | Habilitation options are cochlear implants, American Sign Language. Availability and cost relates to invasiveness of intervention [10, 11]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 47% | Varies with treatment chosen. Educational performance significantly improved [5]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 68% | Educational performance significantly improved [5]. |
| Benefits of early identification | SOME benefits to family and society | 91% | Identification of relatives [3, 12,13,14]. |
| Prevention of mortality | No | 8% | Mortality may be prevented in syndromal cases [15]. Not an issue in most forms. |
| Confirmation of diagnosis | Widely available | 83% | Confirmation of hearing loss is widely available but determination of genetic etiology is less widely available [16]. |
| Acute management | Widely available | 77% | Varies if syndromal or nonsyndromal [1]. |
| Simplicity of therapy | Periodic involvement of a specialist (lack of consensus) (*) | 43% | Varies with treatment chosen [1]. |

**Hearing loss**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | Audiometry |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1354 /2100 | % of max score | 64% |
| Rank: | 75 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Hearing loss tends to score lower since it is a singleton test of a functional response. Because the test is for a phenotype associated with many conditions for which there are varying interventions, cost and availability are similarly variable.

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| | |
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| CONDITION | Hyperbilirubinemia (kernicterus) |
|---|---|
| TYPE of DISORDER | Multifactorial and polygenic |
| ETHNICITY | Panethnic |
| SCREENING METHOD(S) | No test; trancutaneous bilirubinometer in clinical trials [1,2]. |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

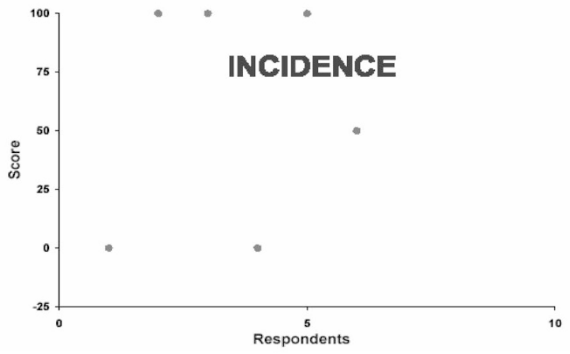
| Responses: | 6 | Valid scores: | 108 | 10% | PubMed references (August 2004) | 1066 |
|---|---|---|---|---|---|---|

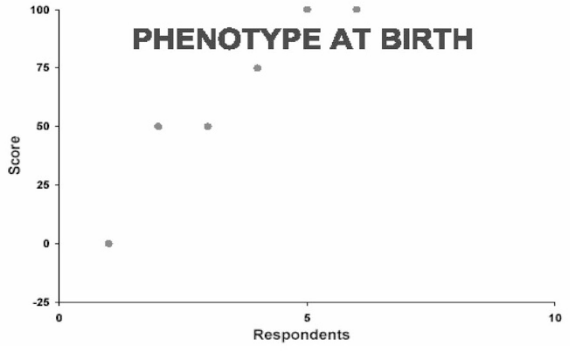
| Gene | *many* | Locus | *many* | OMIM | *many* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | >1:25,000 | 58% | 1:10,000-15,000 newborns have extremely high bilirubin (>30mg/dl) levels [3,4]. Current incidence of kernicterus is not known but is estimated at 1:27,000. |
| Phenotype at birth | Almost never | 63% | Jaundice may be apparent but the severity of the jaundice may be difficult to recognize in some infants [3,4]. |
| Burden if untreated | Profound | 100% | The clinical features of kernicterus vary, and up to 15 percent of infants have no obvious neurologic symptoms. Mortality rate is 4% [5]. |
| The test | | | |
| Screening test | Yes | 83% | No sensitive and specific test has been validated in a large general population [1,2,6-9]. |
| Doable in DBS or by physical method | Yes | 83% | Tests currently being validated are in-nursery measures of bilirubin. |
| High throughput | Yes | 80% | No sensitive and specific test that is validated in a large general population is available [1,2,6,7]. |
| Overall cost <$1 | <$1/test | 80% | No. Based on the cost of reagents. |
| Multiple analytes | No | 0% | No. |
| Secondary targets | No | 0% | Hyperbilirubinemia is associated with a number of disorders. |
| Multiplex platform | No | 0% | No. |
| The treatment | | | |
| Availability & cost | Widely available | 100% | Treatment for hyperbilirubinemia (phototherapy, breast-feeding) is widely available, though treatment for other features seen in forms with specific etiologies may be less widely available [3,4,7,8]. |
| Efficacy of treatment | Potential to prevent ALL negative consequences | 83% | Hyperbilirubinemia is treatable with normal outcome [3,4,7-9]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 100% | The great majority of etiologies of hyperbilirubinemia are treatable with normal outcome [3,4,8]. |
| Benefits of early identification | CLEAR benefits to family and society | 92% | Normal outcomes maximize the potential of individuals to contribute to society. |
| Prevention of mortality | Yes | 100% | Significant reduction in mortality rates [3,5,8]. |
| Confirmation of diagnosis | Widely available | 100% | Diagnostic protocols are widely available [3]. |
| Acute management | Widely available | 100% | Management guidelines are widely available [3,11]. |
| Simplicity of therapy | Primary care, family level | 88% | Management of the great majority of cases is simple [3]. |

**Hyperbilirubinemia (kernicterus)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | 0 |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1584 /2100 | % of max score | 75% |
| Rank: | 0.96 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Increased production of bilirubin, deficiency of hepatic uptake, impaired conjugation of bilirubin, and increased enterohepatic circulation of bilirubin account for most cases of pathologic jaundice in newborn infants [4]. It is recommended that for all infants there be: 1) promotion and support of breast feeding; 2) systematic pre-discharge assessments of risk for hyperbilirubinemia; 3) follow-up of based on the risk assessment; and 4) treatment when indicated. Some etiologies of hyperbilirubinemia require prompt response (exchange transfusion) that implies that this is better managed locally. Primary areas of difference between surveys and literature are in the availability of a population validated test.

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| | |
|---|---|
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| CONDITION | Neuroblastoma |
|---|---|
| TYPE of DISORDER | Genetic Condition |
| ETHNICITY | Panethnic |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

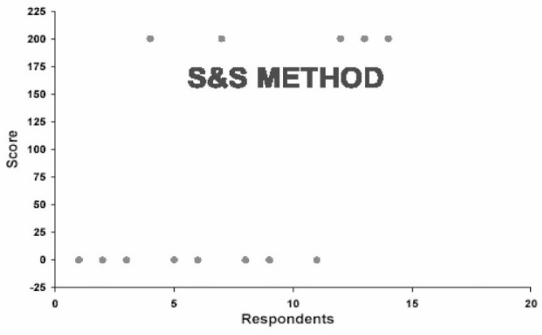
| Responses: | 14 | Valid scores: | 242 | 96% | PubMed references (August 2004) | 21550 |
|---|---|---|---|---|---|---|

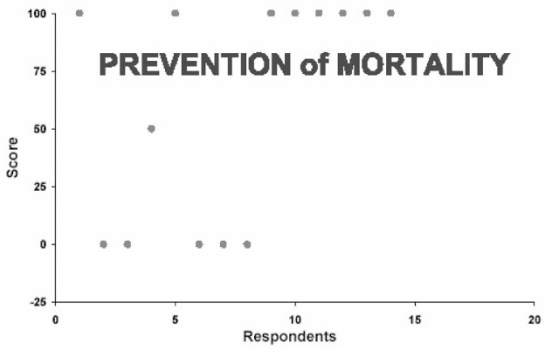
| Gene | *NBS* | Locus | *1p36.3-p36.2* | OMIM | *256700* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:25,000 | 61% | 1:7,000 children [1,2,3]. |
| Phenotype at birth | Almost never | 84% | Median age at diagnosis of this well described condition is 22 months [1]. |
| Burden if untreated | Severe | 70% | Varies with stage of disease. Stages 3 and 4 have a two-year disease-free survival range of 30-40% [1,4,5]. |
| The test | | | |
| Screening test | No | 38% | No (due to poor test performance). 5 - 10% of cases lack elevated urinary catecholamines at age 3 weeks [6,7]. Test lacks sensitivity for those with the most severe forms [6,8] and identifies many with tumors that spontaneously regress [9,10]. |
| Doable in DBS or by physical method | No | 15% | Yes, but test lacks sensitivity [6,8]. |
| High throughput | No | 15% | Yes, but test lacks sensitivity [6,8]. |
| Overall cost <$1 | No (>$1/test) | 8% | Not applicable. |
| Multiple analytes | No | 8% | Not applicable. |
| Secondary targets | No | 8% | Not applicable. |
| Multiplex platform | No | 0% | Not applicable. |
| The treatment | | | |
| Availability & cost | Limited availability | 46% | Chemotherapy, surgery, radiation, bone marrow transplant and stem cell therapy [1,11,12]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 41% | Screening at 3 weeks and 6 months of age [6] and at 1 yr. [8] had no effect on mortality. In 7 million Japanese screened newborns, a marginal decrease in mortality was seen [14]. There was no decrease in advanced disease in older children [9-12]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 50% | Screening at 3 weeks and 6 months of age [6] and at 1 yr. [8] had no effect on mortality. There was no decrease in advanced disease in older children [9-12]. |
| Benefits of early identification | SOME benefits to family and society | 61% | Some rare forms of familial cancer may be identified [1]. |
| Prevention of mortality | Yes | 61% | Screening does not reduce neuroblastoma-associated mortality [6,8]. In 7 million Japanese screened newborns, a marginal decrease in mortality was seen [14]. |
| Confirmation of diagnosis | Limited availability | 64% | Tumor histology showing neural origin or differentiation and staging of tumors requires specialists [11,12]. and NMYC testing is widely available through COG affiliated programs. |
| Acute management | Limited availability | 64% | Tumor staging and chemotherapy, surgery, radiation and other treatments are not widely available [1,11-14]. |
| Simplicity of therapy | Regular involvement of specialist | 29% | Regular involvement of pediatric oncologists is required for management [1]. |

**Neuroblastoma**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 864 /2100 | % of max score | 41% |
| Rank: | 0.22 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Screening of infants for neuroblastoma by measurement of urinary catecholamines led to a doubling of the apparent incidence of neuroblastoma in children without a decrease in advanced disease in older children. Testing for MCYN amplification, usually by FISH methods, is widely available through core laboratories of the Children's Oncology Group, a cooperative cancer study group. Also, tumor staging and treatment is widely available (over 250 institutions across the US that participate in COG trials) [14].

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| CONDITION | Smith-Lemli-Opitz syndrome |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of cholesterol biosynthesis |
| ETHNICITY | More common in Northern Europeans and less common in Asia and Africa. |
| SCREENING METHOD(S) | No test available at the present time |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

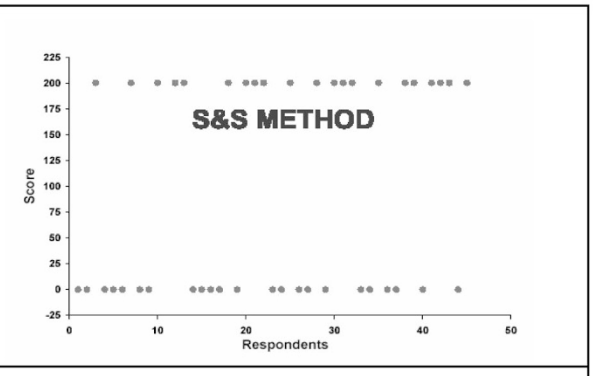
| Responses: | 45 | Valid scores: | 784 | 97% | PubMed references (August 2004) | 462 |
|---|---|---|---|---|---|---|

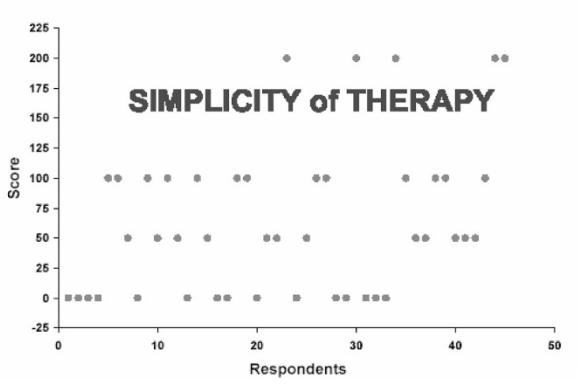
| Gene | *SLOS* | Locus | *11q12-q13* | OMIM | *270400; 268670* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:75,000 | 38% | 1:20,000 - 40,000 [1-3]. |
| Phenotype at birth | <50% of cases | 44% | Newborns may have clefts and other dysmorphology, congenital heart disease. Males may show genital anomalies [4]. |
| Burden if untreated | Profound | 87% | Mental retardation in 95-97% of patients [5]. More than 90% have microcephaly [4,5]. Frequent early lethality in type II [6]. |
| The test | | | |
| Screening test | No (lack of consensus) (*) | 45% | No test has been validated in a large general population in a public health setting. Determination of cholesterol and 7-dehydrocholesterol in dried blood spots is technically feasible by MS/MS and may be applicable to newborn screening [7-10]. |
| Doable in DBS or by physical method | No | 37% | Not applicable. |
| High throughput | No | 20% | Not applicable. |
| Overall cost <$1 | No (>$1/test) | 15% | Not applicable. |
| Multiple analytes | No | 15% | Not applicable. |
| Secondary targets | No | 17% | Not applicable. |
| Multiplex platform | No | 21% | Not applicable. |
| The treatment | | | |
| Availability & cost | Limited availability | 63% | Dysmorphology expertise is of limited availability. Experience with SLO diagnosis, complications and treatment is needed [4,5]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 16% | Clefts, Hirschsprung disease and congenital heart disease can be treated surgically [11]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 29% | Dietary cholesterol supplementation improves behavior, growth and intestinal motility [11-13] but may not enhance developmental progress [14]. |
| Benefits of early identification | SOME benefits to family and society | 60% | Genetic counseling and prenatal diagnosis are available [4,15,16]. |
| Prevention of mortality | No | 18% | Treatment of severely affected patients with cholesterol supplementation may improve initial neonatal mortality. Survival is decreased in those with multiple major malformations [4-6]. |
| Confirmation of diagnosis | Limited availability | 44% | Plasma/serum 7-DHC and cholesterol levels are the gold standard in combination with clinical phenotype to establish diagnosis. Molecular testing can be useful for family studies and genetic counseling [16-19]. |
| Acute management | Limited availability | 46% | SLOS infants are at risk of acute adrenal insufficiency, overwhelming infection and acute respiratory distress syndrome and poor post-surgical wound healing. Experienced surgical management of genital anomalies, congenital heart disease and other features is of limited availability [4]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 32% | Metabolic specialist is required for dietary management [4]. Medical management is complex and requires experience in SLOS. |

**Smith-Lemli-Opitz syndrome**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 759 /2100 | % of max score | 36% |
| Rank: | 0.1 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Smith-Lemli-Opitz syndrome lacks a validated screening test. Incidence of SLO is unclear since there is a discrepancy between carrier rates and identified patients. It remains to be determined if: 1) cases with multiple congenital anomalies are dying without diagnosis; 2) there is an increase in in-utero demises; or 3) mildly affected cases are not being identified for testing.

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| CONDITION | Turner syndrome |
|---|---|
| TYPE of DISORDER | Genetic condition |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

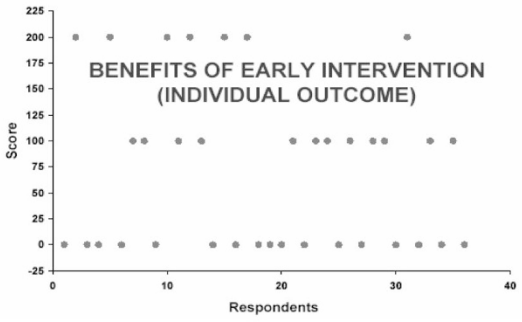
| Responses: | 36 | Valid scores: | 625 | 96% | PubMed references (August 2004) | 5193 |
|---|---|---|---|---|---|---|

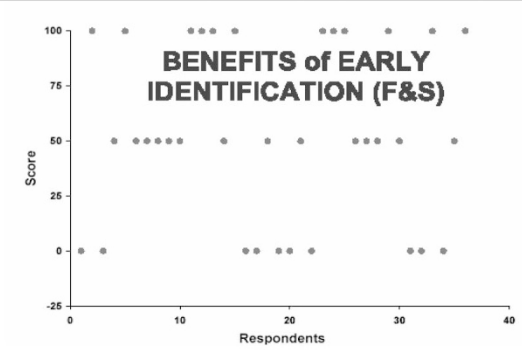
| Gene | *NA* | Locus | *NA* | OMIM | *NA* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | >1:5,000 | 85% | 1:2,500 - 3,000 female births with 45,X and variants (50+% of cases) [1]. |
| Phenotype at birth | <50% of cases | 54% | 20 - 33% are diagnosed as newborns with puffy feet or redundant nuchal skin [2]. |
| Burden if untreated | Moderate | 55% | Varies with karyotype. Short stature, hypoplastic left heart or coarctation of aorta can be lethal; 10% developmentally delayed, 7- 30% risk of gonadoblastoma in 5% of cases who are Y mosaics [2,3,4]. |
| The test | | | |
| Screening test | No | 46% | No studies of TS screening at 24 - 48 hrs post-birth with follicle stimulating hormone (FSH) have been reported. Studies at 5 days and 9 months of age are reported. Some mosaics may achieve menarche and, hence, may be false positive in screening [5,6]. |
| Doable in DBS or by physical method | No | 24% | Yes [5,6]. |
| High throughput | No | 9% | Yes [5,6]. |
| Overall cost <$1 | No (>$1/test) | 3% | Not published. |
| Multiple analytes | No | 16% | No. |
| Secondary targets | No | 19% | No. |
| Multiplex platform | No | 13% | No. |
| The treatment | | | |
| Availability & cost | Limited availability | 50% | Generally available through pediatric endocrinologists [2]. Cost of GH is estimated at $15,000 - $29,000 per centimeter of gained final height. Management of renal and cardiac malformations, recurrent otitis media [7]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 30% | Recombinant human growth hormone improves growth and may, therefore, reduce psychosocial problems. However, evidence of efficacy is inconsistent and not well studied before age 4 yrs. [8,9,10]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome (lack of consensus) (*) | 36% | Improvement in final height in GH treated cases has been variable. Most adults with Turner syndrome cope successfully with the short stature [2,11,12]. |
| Benefits of early identification | SOME benefits to family and society (lack of consensus) (*) | 53% | Some improvement in final height in many [8-11]. |
| Prevention of mortality | No | 23% | Death from cardiac causes is significant and monitoring is recommended [2,4,13]. |
| Confirmation of diagnosis | Widely available | 89% | Chromosome testing is widely available. Mosaicism can complicate predictions of severity [2]. Identification of Y chromosome material is needed to consider gonadoblastoma risk [14]. |
| Acute management | Limited availability | 79% | Management varies with the severity of cardiac defects [16] and renal malformations, diabetes and presence of neoplasia. Well established health supervision protocols exist [2,15]. |
| Simplicity of therapy | Regular involvement of specialist | 32% | Simplicity varies with the severity of the associated syndromal features in the patient. |

**Turner syndrome**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No test |
| Final score | 847 /2100 | % of max score | 40% |
| Rank: | 0.19 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Follicular stimulating hormone as a marker for Turner syndrome was transiently used in screening in France in newborns at 5 days post-birth and at 9 months of age. No studies of FSH screening for TS during the 24 - 48 hrs period after birth have been reported. However, it is reported that the rise in FSH levels is not significant until after 6 -7 days of life.
Most phenotypic features are managed as present and necessary and less dependent on early diagnosis. Early diagnosis informs assessment. Final height may be improved by early diagnosis.

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| CONDITION | Wilson disease |
|---|---|
| TYPE of DISORDER | Genetic condition |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | No test available at the present time |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

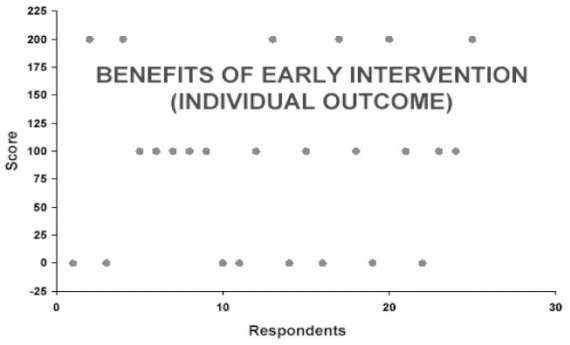
| Responses: | 25 | Valid scores: | 421 | 94% | PubMed references (August 2004) | 3,395 |
|---|---|---|---|---|---|---|

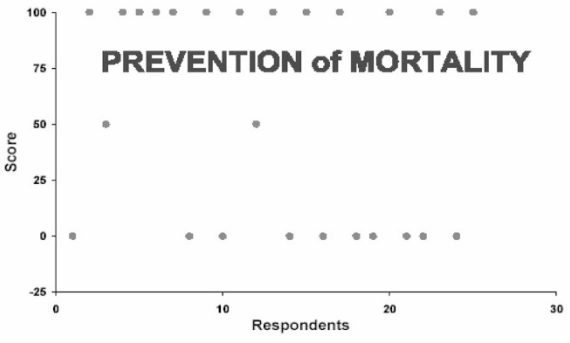
| Gene | *ATP7B* | Locus | *13q14.3-q21.1* | OMIM | *277900* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:50,000 | 51% | 1:30,000 worldwide [1,2]. 1:10,000 in Japan, China and Sardinia [3]. |
| Phenotype at birth | Almost never | 91% | Patients typically present with either liver disease (between 10 - 13 yrs in most cases) or neuropsychiatric disease (usually presenting in the 3rd decade) [2,4,5]. |
| Burden if untreated | Severe | 79% | Neurological form progresses to movement disorders or rigid dystonia and widely variable psychiatric disorders including depression. Hepatic form can lead to liver failure [2,5-10]. |
| The test | | | |
| Screening test | No | 48% | No test has been validated in a large general population in a public health setting. Determination of ceruloplasmin in dried blood spots is technically feasible using an ELISA method and may be applicable to population screening. Pilot studies are in progress in the US and Japan [10,11]. |
| Doable in DBS or by physical method | No | 10% | Yes, but still in pilot testing. |
| High throughput | No | 19% | Yes, but still in pilot testing. |
| Overall cost <$1 | No (>$1/test) | 14% | No. |
| Multiple analytes | No | 0% | No. |
| Secondary targets | No | 0% | No. |
| Multiplex platform | No | 0% | No. |
| The treatment | | | |
| Availability & cost | Limited availability | 61% | Copper chelating agents and zinc to stimulate metallothinein [1,5,6,9,12,13]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 55% | Can prevent disease development in the asymptomatic patients and reduce severity in symptomatic cases. However, there is limited data available from those who are treated as newborns or early childhood [1,5,6,9,12,13]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome (lack of consensus) (*) | 46% | Can prevent disease development in the asymptomatic patients and reduce severity in symptomatic cases [1,5,6,9,12,13]. |
| Benefits of early identification | SOME benefits to family and society | 60% | Genetic counseling and prenatal diagnostics are available [6,13,14]. |
| Prevention of mortality | Yes (lack of consensus) (*) | 56% | Lethal in cases with fulminant hepatic failure if not transplanted [5,6]. |
| Confirmation of diagnosis | Limited availability | 69% | Clinical evaluation including slit lamp to identify Kayser-Fleisher rings; reduced ceruloplasmin; increased liver and urine copper [1,5,6]. DNA testing is available and needed for confirmation in patients and family members [18]. |
| Acute management | Limited availability | 58% | Liver transplantation may be required for fulminant hepatic failure [18,19] and chelating agents and surveillance require involvement of specialists. Well established emergency protocols [6]. |
| Simplicity of therapy | Regular involvement of specialist | 36% | Management of copper levels requires the involvement of specialists [6]. |

**Wilson disease**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 922 /2100 | % of max score | 44% |
| Rank: | 0.24 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

There were differences between the literature and the survey respondents with regard to the efficacy of treatments. There is considerable evidence that treatment of Wilson disease can prevent disease development and reduce the severity of the disease in those already symptomatic. However, there is limited data on treatment of infants and young children and the risks of using zinc or other copper chelating agents and blocking of intestinal absorption in young children are not clear. Evidence-based approaches to understanding the safety and efficacy of the treatments in infants are needed.

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| | |
|---|---|
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| CONDITION | X-Linked adrenoleukodystrophy |
|---|---|
| TYPE of DISORDER | Inborn error of peroxisomal fatty acid oxidation |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | No test available at the present time |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | 38 | Valid scores: | 668 | 98% |
|---|---|---|---|---|

| PubMed references (August 2004) | 1,386 |
|---|---|

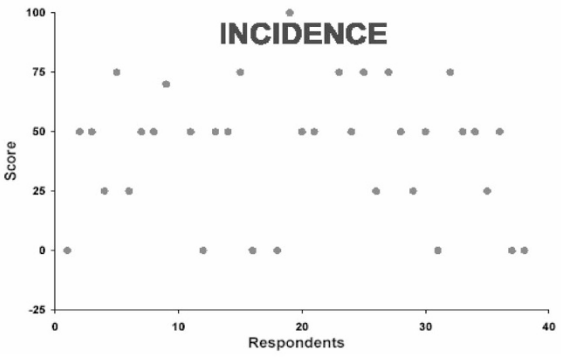
| Gene | *ABCD1* | Locus | *Xq28* | OMIM | *300100* |
|---|---|---|---|---|---|

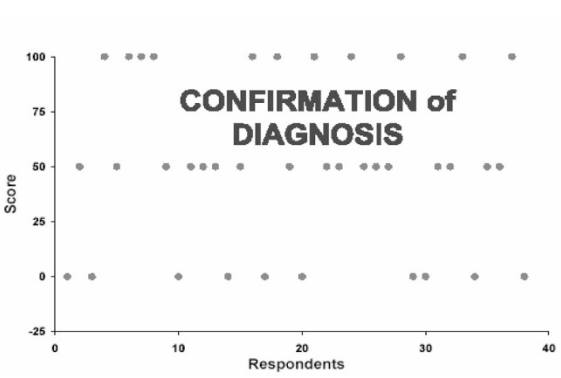
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:50,000 | 43% | 1:17,000 for US males and females combined; 1:20,000 in the US, Canada and France, combined [1]. |
| Phenotype at birth | Almost never | 93% | In childhood form, onset is between 4 - 8 yrs; adrenomeloneuropathy (AMN) form presents in late 20's; Addison only form presents between age 2 and adulthood [2,3]. |
| Burden if untreated | Profound | 92% | In childhood form, progression to total disability within 2 yrs. AMN form shows progressing paraparesis. Significant varability in expression ranging from asymptomatic to severe childhood form [3,4]. |
| The test | | | |
| Screening test | No | 27% | No test has been validated in a large general population in a public health setting. Determination of very long chain fatty acids in dried blood spots is technically feasible but hampered by the presence of VLCFA in filter paper. |
| Doable in DBS or by physical method | No | 32% | No available evidence at the present time. |
| High throughput | No | 17% | No available evidence at the present time. |
| Overall cost <$1 | No (>$1/test) | 11% | No available evidence at the present time. |
| Multiple analytes | No | 22% | No available evidence at the present time. |
| Secondary targets | No | 22% | No available evidence at the present time. |
| Multiplex platform | No | 17% | No available evidence at the present time. |
| The treatment | | | |
| Availability & cost | Not available | 32% | Corticosteroid replacement for adrenal insufficiency. Bone marrow transplantation is useful if initiated before or at onset of cerebral manifestations [6,7]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 19% | 92% five-year survival. However, there is severe disability in most cases [4]. Therapeutic efficacy of Lorenzo's oil continues to be evaluated and debated. It has been reported to have a preventive effect in asymptomatic patients. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 25% | Corticosteroid replacement for adrenal insufficiency; bone marrow transplantation for early cerebral disease; and supportive care. Lorenzo's oil may be preventive of cerebral disease [2-4,14,15] . |
| Benefits of early identification | SOME benefits to family and society | 62% | Genetic counseling and prenatal diagnosis are available [2,8-10]. |
| Prevention of mortality | Not available | 25% | Corticosteroid replacement for adrenal insufficiency may be life-saving. Bone marrow transplantation shows improved 5-year survival [13]. |
| Confirmation of diagnosis | Limited availability | 51% | Serum VLCFA by GC/MS or MS/MS. Should be done by labs with experience in the biochemical diagnosis of X-ALD. DNA testing may be informative and is available and reliable [2,3,8,9]. |
| Acute management | Limited availability | 40% | Corticosteroids for adrenal insufficiency; bone marrow transplant is not usually part of acute management since it is of limited benefit after onset of cerebral disease [3]. |
| Simplicity of therapy | Regular involvement of specialist | 13% | Corticosteroids can be managed by most physicians. Bone marrow transplantation requires specialized teams. Supportive care and coordination require specialist involvement [2]. |

**X-Linked adrenoleukodystrophy**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 705 /2100 | % of max score | 34% |
| Rank: | 0.06 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Childhood form accounts for 35% of cases. Adrenomyeloneuropathy (AMN) form accounts for 40 - 45% of cases; "Addisons only" form accounts for 10% of cases; 5 - 10% of cases have a variable phenotype. The therapeutic efficacy of Lorenzo's oil continues to be evaluated and debated. There are limited reports of potential efficacy, but a randomized placebo controlled clinical trial for childhood ALD has not been done to date. Lovastatin and 4-phenylbutyrate have been proposed as therapeutic agents, but their clinical efficacy has not been tested.

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# AMINO ACID DISORDERS

| CONDITION | Argininemia |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism (Urea Cycle Disorder) |
| ETHNICITY | Panethnic, no known ethic differences. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 16 of 51 states, 23% of annual births (August 2004) |

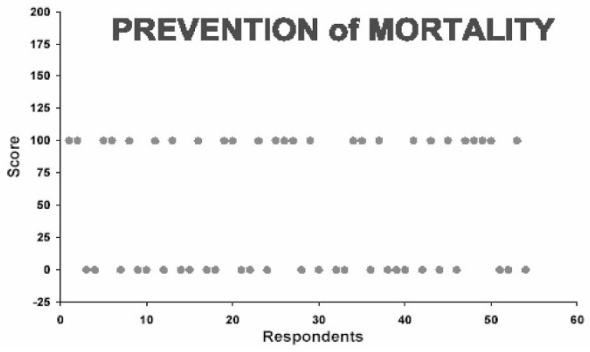
| Responses: | 54 | Valid scores: | 950 | 98% | PubMed references (August 2004) | 39 |
|---|---|---|---|---|---|---|

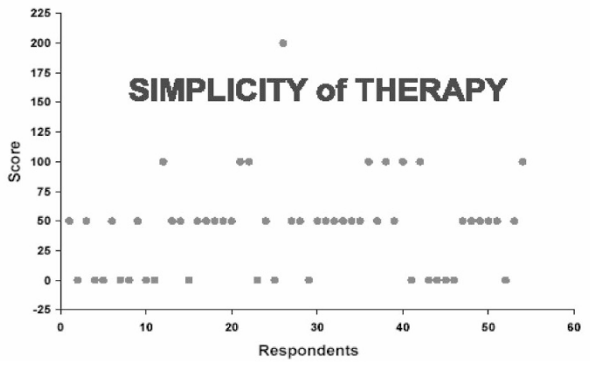
| Gene | *ARG1* | Locus | *6q23* | OMIM | *207800* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 2% | Not known; estimated at 1:360,000 births [1]. |
| Phenotype at birth | Almost never | 89% | Variable age of onset of severe symptoms; and usually after neonatal period though many are suspicious as neonates [2,3]. |
| Burden if untreated | Severe | 83% | Elevated arginine leading to progressive spastic quadriplegia and mental retardation; hyperammonemic episodes are rarer and milder than in other urea cycle disorders [1,4-6]. |
| The test | | | |
| Screening test | Yes | 78% | Amino acid profiling by MS/MS may not be of adequate sensitivity prior to 48 hrs. after birth [7]. |
| Doable in DBS or by physical method | Yes | 83% | See [7]. |
| High throughput | Yes | 73% | 500-1,000 specimens per day [7]. |
| Overall cost <$1 | No (>$1/test) | 49% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [8]. |
| Multiple analytes | Yes | 60% | Yes, arginine and arginine:ornithine ratio are elevated but may not be adequately sensitive in the 48 hrs. after birth. |
| Secondary targets | No | 45% | No. |
| Multiplex platform | Yes | 53% | For comprehensive review, see [5]. |
| The treatment | | | |
| Availability & cost | Limited availability | 50% | Protein restricted diet and sodium benzoate or phenylbutyrate is available but at high cost [4,5,9-12]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 37% | Natural history with treatment is poorly understood [5,9]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 58% | Treatment is expected to reduce neurological dysfunction [5,9-12]. |
| Benefits of early identification | CLEAR benefits to family and society | 75% | Identification of affected relatives; genetic counseling available; prenatal diagnosis available [5,13]. |
| Prevention of mortality | No (lack of consensus) (*) | 49% | See [5,9]. |
| Confirmation of diagnosis | Limited availability | 62% | Plasma amino acid analysis showing markedly elevated arginine and urine orotic acid analysis (markedly elevated). Arginase assay in RBC is of limited availability [5,14]. |
| Acute management | Limited availability | 49% | Metabolic specialist needed. See [4,5]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 22% | Restriction of protein intake and supplementation with mixtures of amino acids excluding arginine; lysine and ornithine supplementation, conjugating agents [4,12]. |

**Argininemia**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1151 /2100 | % of max score | 55% |
| Rank: | 0.48 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Arginase deficiency is a clinically significant condition detected by MS/MS. On the basis of a limited knowledge of natural history, it is considered a secondary screening target. Some experts involved in validation considered that treatment efficacy was similar to that of argininosuccinate synthase deficiency such that it should be a primary target of newborn screening.

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| CONDITION | Argininosuccinic acidemia |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism (urea cycle defect) |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 21 of 51 states, 31% of annual births (August 2004) |

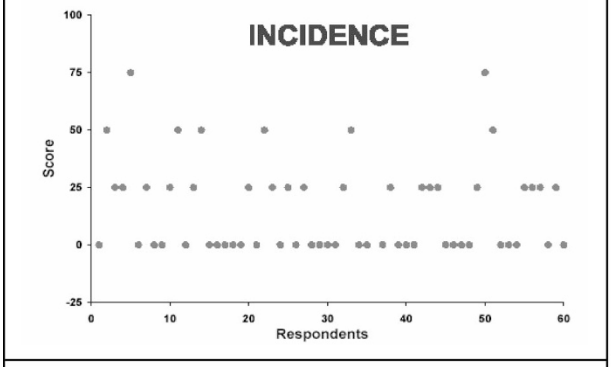
| Responses: | 60 | Valid scores: | 1,053 | 98% | PubMed references (August 2004) | 242 |
|---|---|---|---|---|---|---|

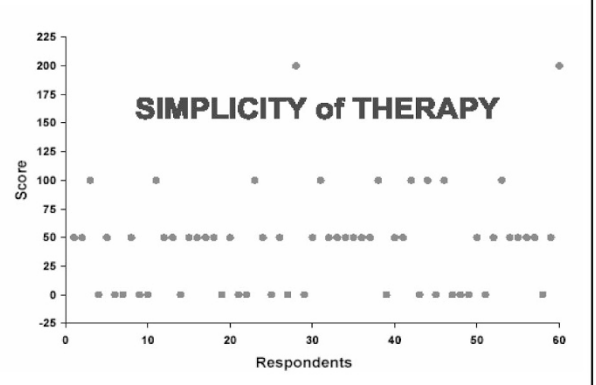
| Gene | *ASL* | Locus | *7cen-q11.2* | OMIM | *207900* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 16% | Not known; estimated at 1:70-180,000 births. |
| Phenotype at birth | <25% of cases | 74% | Rarely presents in first 48 hrs. [2, 3]. |
| Burden if untreated | Profound | 92% | Rapid onset hyperammonemia leading to lethargy, seizures and to coma and death, though less commonly than other urea cycle disorders [2-6]. |
| The test | | | |
| Screening test | Yes | 78% | Amino acid profiling by MS/MS for citrulline, SRM scan for argininosuccinic acid [7]. |
| Doable in DBS or by physical method | Yes | 84% | Yes, see [7]. |
| High throughput | Yes | 73% | 500-1,000 specimens per day [7]. |
| Overall cost <$1 | <$1/test | 55% | Cost likely higher if MS/MS is used to screen only for a few diseases [8]. |
| Multiple analytes | Yes | 60% | Citrulline, argininosuccinic acid [7]. |
| Secondary targets | No | 49% | Citrullinemia, citrin deficiency [7]. |
| Multiplex platform | Yes | 58% | For comprehensive review see [7]. |
| The treatment | | | |
| Availability & cost | Limited availability | 48% | Special formulas are relatively expensive. Arginine supplementation [1-6,9]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 42% | Natural history with treatment is poorly understood. Mortality is improved but morbidity remains significant, particularly in neonatal onset cases [6]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes outcome | 75% | Mortality is improved but morbidity remains significant, particularly in neonatal onset cases [6]. |
| Benefits of early identification | CLEAR benefits to family and society | 81% | Genetic counseling and prenatal diagnosis are available [2,10]. |
| Prevention of mortality | Yes | 85% | Acute episodes are potentially life-threatening [2,3,9]. |
| Confirmation of diagnosis | Limited availability | 64% | Amino acid analysis is generally adequate for diagnoses. Red cell AS lyase enzymology is of limited availability [1,2,5]. Metabolic physicians are of limited availability. |
| Acute management | Limited availability | 48% | Requires metabolic specialist and multidisciplinary team [2, 6,9]. |
| Simplicity of therapy | Regular involvement of a specialist (lack of consensus) (*) | 23% | Metabolic specialists in a multidisciplinary team[2,6,9]. |

**Argininosuccinic acidemia**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1263 /2100 | % of max score | 60% |
| Rank: | 0.65 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Argininosuccinic acidemia meets the criteria for inclusion in the uniform panel. The test is sensitive and specific, secondary targets can be detected, and treatment is available to reduce morbidity and mortality

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| | |
|---|---|
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| CONDITION | Defects of biopterin cofactor biosynthesis |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism |
| ETHNICITY | BH4 abnormalities more common in Saudi Arabia, Brazil, Taiwan and Turkey [1]. |
| SCREENING METHOD(S) | BIA, tandem mass spectrometry (MS/MS), fluorometry and enzyme assays |
| NBS STATUS in the US | Screened for in 51 of 51 states, 100% of annual births (August 2004) |

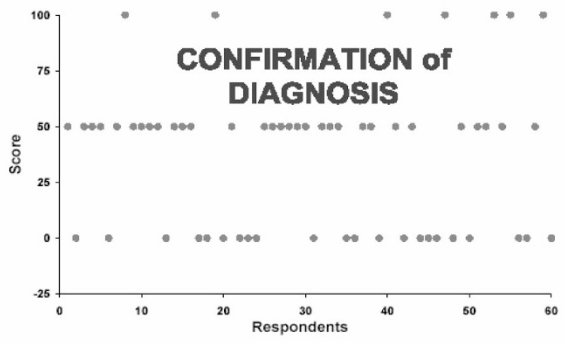
| Responses: | 60 | Valid scores: | 1,047 | 97% | PubMed references (August 2004) | 3,132 |
|---|---|---|---|---|---|---|

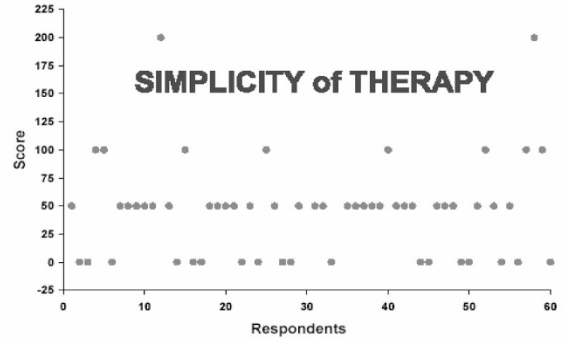
| Gene | *GCH1 PTS* | Locus | *14q22; 1-q22.2; 11q22.3-q23.3* | OMIM | *233910; 261640* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 3% | Incidence not known [1,2]. |
| Phenotype at birth | Almost never | 90% | Symptoms usually manifest at about 4 months [1,2]. Low birth weight in 6-pyruvoyltetrahydropterin synthase (PTPS) [3]. |
| Burden if untreated | Profound | 92% | 80% of cases severe [1,2,4-6]. |
| The test | | | |
| Screening test | Yes | 85% | MS/MS for hyperphenylalaninemia-associated types [7,8]. |
| Doable in DBS or by physical method | Yes | 81% | Yes, see [7,8]. |
| High throughput | Yes | 67% | Up to 500 - 1,000 specimens per day [8]. |
| Overall cost <$1 | <$1/test | 49% | Cost likely higher if MS/MS is used to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [9]. |
| Multiple analytes | Yes | 59% | Yes, see [8]. |
| Secondary targets | Yes | 62% | Yes, see [8]. |
| Multiplex platform | Yes | 60% | Yes, see [8]. |
| The treatment | | | |
| Availability & cost | Limited availability | 42% | BH4 to control hyperphenylalaninemia and neurotransmitter replacement. Diet management/monitoring require metabolic disease physician [1,2]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 39% | Slows neurological deterioration and reduces mortality [10-12]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 66% | Slows neurological deterioration and reduces mortality [10-12]. |
| Benefits of early identification | SOME benefits to family and society | 78% | Genetic counseling and prenatal diagnosis available [13]. Molecular testing is available [15]. |
| Prevention of mortality | No | 48% | No mortality [1,2,12]. |
| Confirmation of diagnosis | Only in a few centers (lack of consensus) (*) | 38% | Diagnostic tests (pterins and dihydropteridine reductase to confirm) for HPA are to distinguish benign hyperphenylalaninemia from clinically significant forms [14]. Limited laboratory availability. Metabolic disease physicians for diet management and monitoring. |
| Acute management | Only in a few centers | 38% | Dietary management and monitoring as well as neurotransmitter replacement require metabolic physicians and other specialists [1,2]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 23% | Dietary management and monitoring as well as neurotransmitter replacement require metabolic physicians and other specialists [1,2]. |

**Defects of biopterin cofactor biosynthesis**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1174 /2100 | % of max score | 56% |
| Rank: | 0.53 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Two genes: GTPCH (guanosine triphosphate cyclohydrolase-1) deficiency is very rare. 57% of BH4 abnormalities involve PTPS (6-pyruvoyltetrahydropterin synthase) deficiency. These conditions are closely involved in the differential diagnosis of hyperphenylalaninemia.

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| 15 | Thöny B, Blau, N. Mutations in the GTP cyclohydrolase I and 6-pyruvoyl-tetrahydropterin synthase genes. Hum Mutat 1997;10:11-20. |
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| CONDITION | Defects of biopterin cofactor regeneration |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | BIA, DELFIA, tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 51 of 51 states, 100% of annual births (August 2004) |

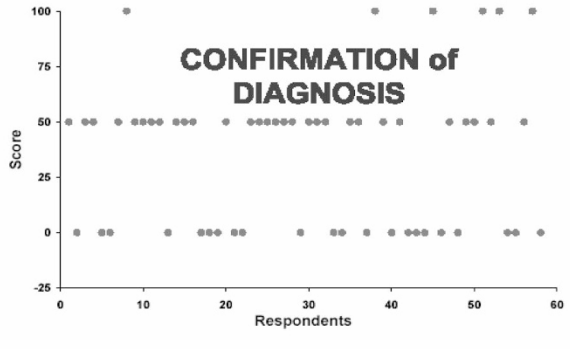
| Responses: | 58 | Valid scores: | 1,011 | 97% | PubMed references (August 2004) | 3132 |
|---|---|---|---|---|---|---|

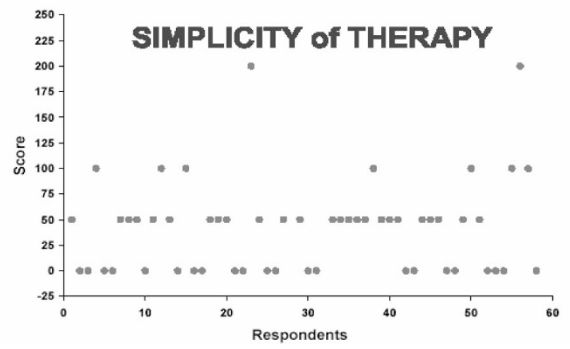
| Gene | *QDPR PCBD* | Locus | *4p15.31 10q22* | OMIM | *261630 264070* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 1% | Incidence not known [1, 2]. |
| Phenotype at birth | Almost never | 88% | Transient neurologic impairment may be apparent in PCD [3]. Symptoms usually appear around 4 months of age [4-7]. |
| Burden if untreated | Profound | 90% | No significant long-term abnormalities in PCD. Seizures and neurodegeneration in DHPR as in GTPCH and PTPS [4-7]. |
| The test | | | |
| Screening test | Yes | 86% | MS/MS for HPA associated types [8, 9]. |
| Doable in DBS or by physical method | Yes | 88% | Yes, see [8, 9]. |
| High throughput | Yes | 66% | Up to 500 - 1,000 specimens per day [9]. |
| Overall cost <$1 | No (>$1/test) | 45% | Cost likely higher if MS/MS is used to screen for 1 - 3 conditions only (CT, MI, NY, RI, VA, WA) [10]. |
| Multiple analytes | Yes | 56% | Yes, see [9]. |
| Secondary targets | Yes | 58% | Yes, see [9]. |
| Multiplex platform | Yes | 55% | Yes, see [9]. |
| The treatment | | | |
| Availability & cost | Limited availability | 41% | BH4 for DHPR to control hyperphenylalaninemia. Dietary management and neurotransmitter replacement. Monitoring of HPA and BH4 require metabolic disease physician [11-12]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 38% | Slows neurological deterioration and reduces mortality [11-12]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 64% | Slows neurological deterioration and reduces mortality [11-12]. |
| Benefits of early identification | CLEAR benefits to family and society | 75% | Genetic counseling, DNA testing and prenatal diagnosis available [13,14]. |
| Prevention of mortality | No | 49% | Reduces mortality [11-12]. |
| Confirmation of diagnosis | Only in a few centers (lack of consensus) (*) | 36% | HPA diagnostic tests distinguish benign hyperphenylalaninemia from clinically significant forms. [12] Limited availability of lab and metabolic physicians. |
| Acute management | Only in a few centers | 39% | Dietary management and monitoring as well as neurotransmitter replacement require metabolic physicians and other specialists [1, 2]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 21% | Dietary management and monitoring as well as neurotransmitter replacement require metabolic physicians and other specialists [1, 2]. |

**Defects of biopterin cofactor regeneration**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1146 /2100 | % of max score | 55% |
| Rank: | 0.46 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Two genes: PCD (pterin-4-α-carbinolamine dehydratase) deficiency is very rare. DHPR (dihydropteridine reductase) deficiency is more common than PCD. Patient registry is available through the tetrahydrobiopterin home page [16]. These conditions are closely involved in the differential diagnosis of Hyperphenylalaninemia.

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| 14 | Dianzani I et al. Dihydropteridine reductase deficiency: physical structure of the QDPR gene, identification of two new mutations and genotype-phenotype correlations. Hum Mutat 1998;12:267-273. |
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| 16 | Tetrahydrobiopterin Home Page. http://www.bh4.org. |

| CONDITION | Carbamylphosphate synthetase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error of metabolism, amino acid disorder |
| ETHNICITY | No known ethnic differences |
| SCREENING METHOD(S) | No sensitive and specific test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (as August 2004) |

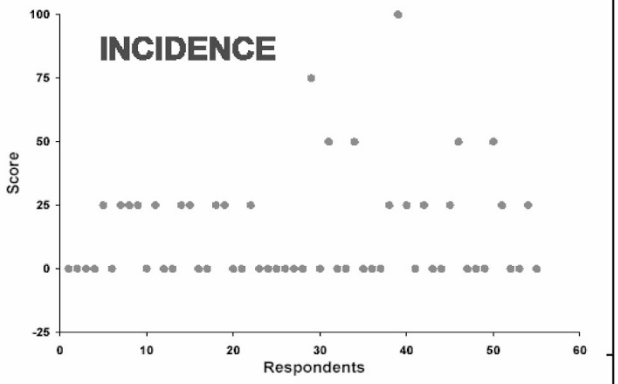
| Responses: | 55 | Valid scores: | 969 | 98% | PubMed references (August 2004) | 515 |
|---|---|---|---|---|---|---|

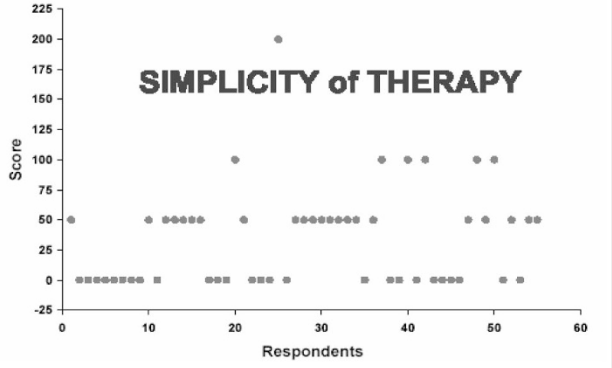
| Gene | *CPS1* | Locus | *2q35* | OMIM | *608307* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 14% | 1:62,000 [1]. |
| Phenotype at birth | <25% of cases | 68% | Early neonatal onset is common [2, 3]. |
| Burden if untreated | Profound | 97% | Developmental delay and mental retardation due to hyperammonemia. Lethal without liver transplantation in neonatal-onset cases [3,4]. |
| The test | | | |
| Screening test | No | 17% | No. Monitoring of low citrulline levels lacks sensitivity and specificity. |
| Doable in DBS or by physical method | No | 29% | No test. |
| High throughput | No | 22% | No test. |
| Overall cost <$1 | No (>$1/test) | 18% | No test. |
| Multiple analytes | No | 19% | No test. |
| Secondary targets | No | 23% | CPS, NAGS and OTC deficiency have identical biochemical phenotypes by amino acid analysis. |
| Multiplex platform | No | 21% | No test. |
| The treatment | | | |
| Availability & cost | Limited availability | 38% | Protein restricted diet [6,7]; sodium benzoate, phenylacetate or phenylbutyrate [8,9]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 38% | Natural history with treatment is poorly understood. Reduced morbidity and mortality [1,3]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 55% | Natural history with treatment is poorly understood. Mortality improved but morbidity remains significant, particularly in neonatal onset cases [1,3]. |
| Benefits of early identification | CLEAR benefits to family and society | 80% | Genetic counseling and prenatal diagnosis are available [3, 10,11]. |
| Prevention of mortality | Yes | 83% | Yes, with liver transplantation in severe cases [1,3-5,12]. |
| Confirmation of diagnosis | Limited availability | 45% | Plasma amino acid analysis (high GLN and ALA, low CIT) and urine orotic acid. Enzyme assay in liver, rectum, and duodenal tissue [5]. |
| Acute management | Limited availability | 44% | Requires metabolic specialist and multidisciplinary team [3, 5,9]. |
| Simplicity of therapy | Regular involvement of specialist | 17% | Metabolic specialists in a multidisciplinary team [3,5,9]. |

**Carbamylphosphate synthetase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No test |
| Final score | 833 /2100 | % of max score | 40% |
| Rank: | 0.17 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

The amino acid profile by MS/MS cannot detect this condition consistently. Although four states (IA, MS, ND, and PA) have included CPS in their program (none have included OTC deficiency), there is no objective evidence at this time in support of the availability of a screening test. However, if a newborn is found to have significantly low citrulline, CPS and OTC deficiency are clearly clinically significant conditions and as such should be reported as soon as possible. There is a high false positive rate associated with low citrulline levels due to low protein intake in neonates.

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| CONDITION | Citrullinemia (argininosuccinate synthase deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error of metabolism, amino acid disorder (urea cycle defect) |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

| Responses: | 63 | Valid scores: | 1,111 | 98% | PubMed references (August 2004) | 286 |
|---|---|---|---|---|---|---|

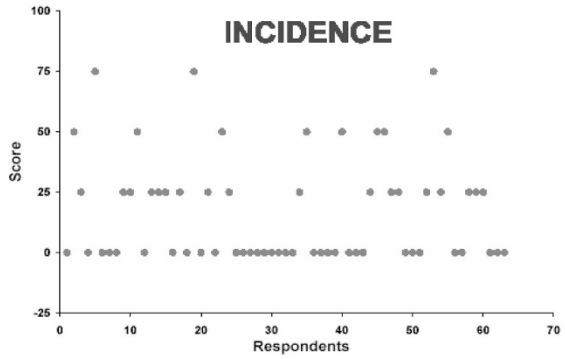
| Gene | *CTLN1* | Locus | *9q34* | OMIM | *215700* |
|---|---|---|---|---|---|

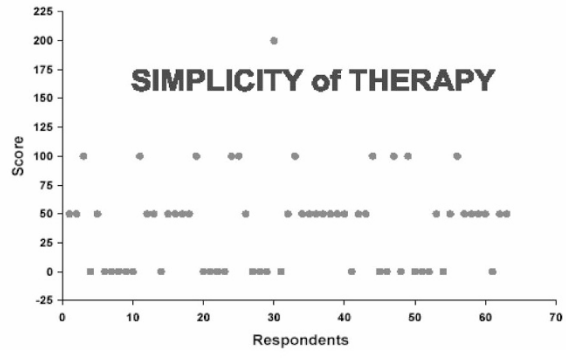
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 17% | 1:57,000 births [1]. |
| Phenotype at birth | <25% of cases | 71% | Newborns are usually asymptomatic in first 24-72 hrs. [2,3]. |
| Burden if untreated | Profound | 94% | Hyperammonemia and encephalopathy leading to coma and death in most undiagnosed cases. Variability based on residual enzyme activity [3]. |
| The test | | | |
| Screening test | Yes | 81% | MS/MS neutral loss scan of m/z 102 or MRM m/z 119 for amino acid profiling. Primary marker is citrulline [4]. |
| Doable in DBS or by physical method | Yes | 87% | Yes, see [5]. |
| High throughput | Yes | 77% | 500-1,000 specimens per day [5]. |
| Overall cost <$1 | <$1/test | 58% | Cost likely higher if MS/MS is used to screen only for a few diseases [6]. |
| Multiple analytes | Yes | 62% | ARG, ASA, CIT-II, but only for the purpose of differential diagnosis [4,5]. |
| Secondary targets | No | 48% | Citrin deficiency, argininosuccinic aciduria [4]. |
| Multiplex platform | Yes | 62% | For comprehensive review see [4]. |
| The treatment | | | |
| Availability & cost | Limited availability | 50% | Special formulas are relatively expensive. Arginine supplementation. Treatment with sodium benzoate, phenylacetate and phenylbutyrate [3]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 40% | Outcome largely dependent on neurologic damage prior to treatment and level of metabolic control [7]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 74% | Reduction of morbidity and mortality by aggressive treatment of acute episodes [7,10,11]. |
| Benefits of early identification | CLEAR evidence of benefits to family & society | 77% | Identification of relatives; genetic counseling available; prenatal diagnosis available in a few centers [1]. |
| Prevention of mortality | Yes | 80% | Acute episodes are potentially life-threatening [7]. |
| Confirmation of diagnosis | Limited availability | 60% | Plasma amino acids, in vitro assay of argininosuccinate synthetase activity. DNA analysis possible, allelic heterogeneity in US [5]. |
| Acute management | Limited availability | 50% | Conjugating agents for acute episodes of hyperammonemia requires a multidisciplinary team [2,3]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 21% | Requires metabolic specialist and multidisciplinary team that can be of limited availability [2,3]. |

**Citrullinemia (argininosuccinate synthase deficiency)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1266 /2100 | % of max score | 60% |
| Rank: | 0.66 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Citrullinemia meets the criteria for inclusion in the uniform panel. The test is sensitive and specific, secondary targets can be detected, and treatment is available to reduce morbidity and mortality.

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| | |
|---|---|
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| CONDITION | Citrullinemia type II (citrin deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error of metabolism, amino acid disorder |
| ETHNICITY | Great majority of reported cases are from Japan [1]. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

| Responses: | 38 |
|---|---|

| Valid scores: | 638 | 93% |
|---|---|---|

| PubMed references (August 2004) | 20 |
|---|---|

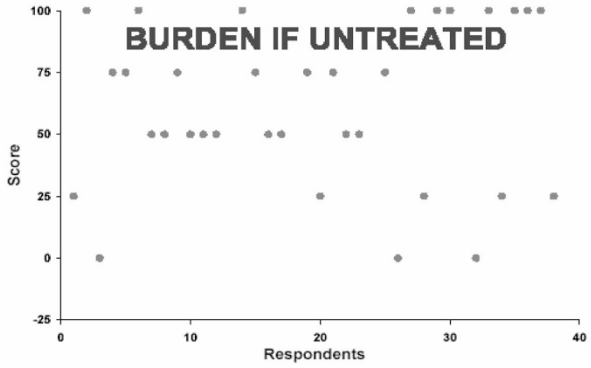
| Gene | *CTLN2* | Locus | *7q21.3* | OMIM | *603471 605814* |
|---|---|---|---|---|---|

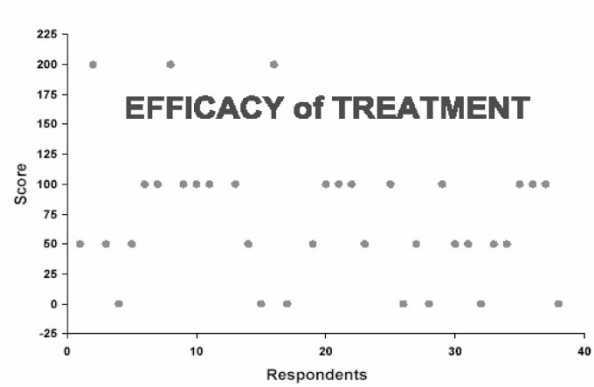
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 4% | Incidence unknown. Most cases from Japan where the incidence is estimated at 1:100,000 though carrier testing suggests an incidence of 1:20,000 [1,3,11,14]. |
| Phenotype at birth | Almost never | 86% | Neonatal form usually presents between 1 - 5 months. [2] Adult form usually presents between ages 11 - 64 yrs. [1, 3]. |
| Burden if untreated | Severe (lack of consensus) (*) | 62% | Neonatal form is managed by protein restriction and may resolve[4]. Adult-onset form progresses to death [1]. |
| The test | | | |
| Screening test | Yes | 58% | MS/MS neutral loss scan of m/z 102 for amino acid profiling. SRM detection is also used. Primary marker is citrulline [5]. |
| Doable in DBS or by physical method | Yes | 69% | Yes, see [5]. |
| High throughput | Yes | 63% | 500 - 1,000 specimens per day [5]. |
| Overall cost <$1 | No (>$1/test) | 46% | Cost likely higher if MS/MS is used to screen only for a few diseases [6]. |
| Multiple analytes | Yes | 59% | Yes, see [5]. |
| Secondary targets | No | 46% | Yes, see [5]. |
| Multiplex platform | Yes | 54% | Yes, see [5]. |
| The treatment | | | |
| Availability & cost | Limited availability | 47% | Liver transplantation in adult-onset form is less available and more costly than protein restricted diet of neonatal form [7, 8]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (lack of consensus) (*) | 36% | Dietary treatment is of unknown benefit. Liver transplantation improves mental outcomes [7, 8, 9]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes outcome | 40% | Liver transplantation improves mental outcomes and reduces mortality [7, 8, 9]. |
| Benefits of early identification | SOME benefits to family and society | 54% | Genetic counseling and prenatal diagnosis are available [10]. |
| Prevention of mortality | Yes | 56% | Liver transplantation significantly reduces mortality [7, 8, 9]. |
| Confirmation of diagnosis | Limited availability | 53% | Elevated citrulline. Mutation analysis is not widely available [3, 11]. |
| Acute management | Limited availability | 46% | Hyperammonemia requires metabolic specialist for protein restricted diet and control of ammonia levels [1,13]. |
| Simplicity of therapy | Regular involvement of specialist | 21% | Dietary management and monitoring requires metabolic specialist [1,13]. |

**Citrullinemia type II (citrin deficiency)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1001 /2100 | % of max score | 48% |
| Rank: | 0.28 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Neonatal and late childhood to adult-onset forms are described. Newly discovered condition, very limited knowledge of natural history. This is a clinically significant condition detected by acylcarnitine profiling to be included in the differential diagnosis of primary targets.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| CONDITION | Homocystinuria cystathionine β-synthase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism |
| ETHNICITY | Higher incidence in Ireland, Australia, Great Britain; lower in Japan. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 30 of 51 states, 51% of annual births (August 2004) |

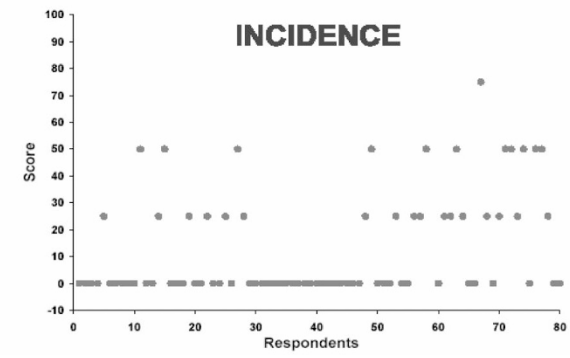
| Responses: | 80 | Valid scores: | 1,372 | 95% | PubMed references (August 2004) | 1437 |
|---|---|---|---|---|---|---|

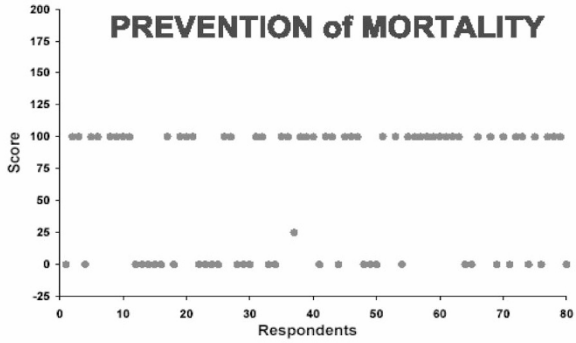
| Gene | *CBS* | Locus | *21q22.3* | OMIM | *236200* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 13% | 1:343,650 in US newborn screens in 12,027,751 newborns [1]. However, molecular studies indicate an incidence of 1:6,000-83,000 due to missed B6-responders [2-4]. |
| Phenotype at birth | Almost never | 91% | Ectopia lentis is rarely apparent in neonates but may become apparent near two years of age [5-7]. |
| Burden if untreated | Profound | 78% | Thromboembolism, developmental delay and mental retardation (about 50%) are typical [5-7]. |
| The test | | | |
| Screening test | Yes | 81% | MS/MS [8,9]. Homocysteine can be detected in a second tier test. |
| Doable in DBS or by physical method | Yes | 95% | Yes, see [9]. |
| High throughput | Yes | 82% | Up to 500-1,000 specimens per day [9]. |
| Overall cost <$1 | <$1/test | 65% | Cost likely higher if MS/MS is used to screen for 1 - 3 conditions only (CT, MI, NY, RI, VA, WA) [10]. |
| Multiple analytes | Yes | 69% | No, only methionine [9]. |
| Secondary targets | Yes | 57% | In addition to CBS deficiency, homocystinuria may be due to a variety of genetic defects affecting 5-methyltetrahydrofolate-dependent methylation of homocysteine [11]. Elevated methionine is also associated with hypermethioninemia [6]. |
| Multiplex platform | Yes | 63% | Yes, see [9]. |
| The treatment | | | |
| Availability & cost | Limited availability | 71% | Establish pyridoxine responsiveness. Amino acid monitoring and dietary management require a metabolic disease physician [14]. Betaine as an adjunct [6,13]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 46% | Risk of thromboembolic events are reduced. Occurrence of mental retardation appears reduced. Long-term outcome studies have been reported [7,12,13]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes outcome | 68% | Long-term outcome studies have been reported. Risk of thromboembolic events are reduced. Occurrence of mental retardation seems to be reduced [7,12,13]. |
| Benefits of early identification | CLEAR benefits to family and society | 79% | Genetic counseling is available. At risk carrier relatives are identified [6]. |
| Prevention of mortality | Yes (lack of consensus) (*) | 60% | Reduction of thromboembolism risk improves mortality [13]. |
| Confirmation of diagnosis | Limited availability | 76% | Plasma and urine amino acid analysis requires a metabolic disease physician [14, 15]. CBS activity can be measured. Mutation analysis is available. |
| Acute management | Limited availability | 61% | Pyridoxine treatment to prevent thromboembolism [6]. |
| Simplicity of therapy | Periodic involvement of specialist | 40% | Dietary management, betaine administration, and monitoring require metabolic physician [6]. |

**Homocystinuria cystathionine β-synthase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | NO |
| Final score | 1357 /2100 | % of max score | 65% |
| Rank: | 0.77 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

B6 responsive and nonresponsive subtypes exist. Since methionine is the analyte tested, CBS deficiency is the form of homocystinuria targeted by screening for elevated methionine levels. Screening for homocystinuria has a lower sensitivity than does screening for amino acidurias and therefore requires special attention in result interpretation. Discrepancies between molecular and biochemical studies partly relate to failure to detect CBS-deficient B6-responders by screening for hypermethininemia. It was because homocystinuria is a potentially treatable condition and that other forms of liver disease detected by the screening may also be treatable that it was included in the core panel.

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| | |
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| CONDITION | Hypermethioninemia (MAT I/III Deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error of metabolism, amino acid disorder |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

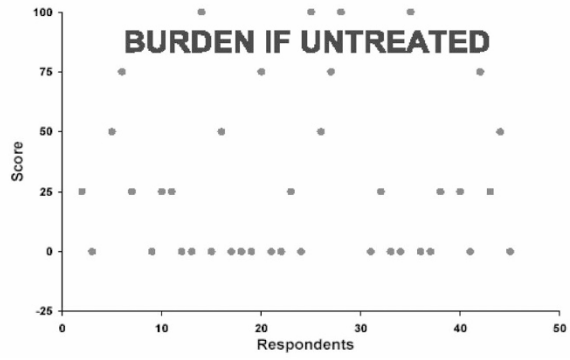
| Responses: | 45 | Valid scores: | 732 | 90% | PubMed references (August 2004) | 59 |
|---|---|---|---|---|---|---|

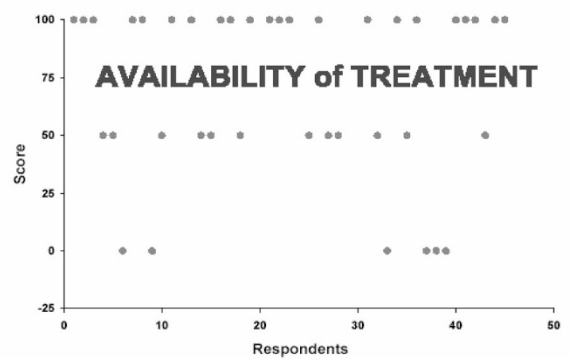
| Gene | *MAT1A* | Locus | *10q22* | OMIM | *250850* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 11% | Incidence not known. Great majority of cases were found through newborn screening for homocystinuria [1]. |
| Phenotype at birth | Almost never | 94% | Not apparent at birth. Great majority of cases were found through newborn screening for homocystinuria [1]. |
| Burden if untreated | Mild | 29% | Mild MAT I/III deficiencies (e.g. R264H heterozygotes) show no associated clinical manifestation. There is evidence of brain demyelination later in life [2]. |
| The test | | | |
| Screening test | Yes | 86% | Initially done by BIA [3] MS/MS [4,5]. |
| Doable in DBS or by physical method | Yes | 91% | Yes, see [4,5]. |
| High throughput | Yes | 81% | Up to 500 - 1,000 specimens per day [5]. |
| Overall cost <$1 | <$1/test | 63% | Cost likely higher if MS/MS is used to screen for 1 - 3 conditions only (CT, MI, NY, RI, VA, WA) [6]. |
| Multiple analytes | Yes | 67% | Methionine [5]. |
| Secondary targets | Yes | 65% | Yes. Cystathionine ß-synthase deficiency; glycine N-methyltransferase deficiency, S-adenosylhomocysteine hydrolase deficiency, and tyrosinemia I. Generalized liver disease may also be identified [2,5,7-9]. |
| Multiplex platform | Yes | 71% | Yes, see [4,5]. |
| The treatment | | | |
| Availability & cost | Limited availability | 70% | S-adenosylmethionine and monitoring of methionine levels require specialist [1]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 34% | Outcome data is limited to determine if brain demyelination is preventable/reversible with early treatment [2,10,12]. |
| Benefits of early intervention | NO evidence that early intervention optimizes individual outcome | 23% | Outcome data is limited to determine if brain demyelination is preventable/reversible with early treatment [2,10,12]. |
| Benefits of early identification | SOME benefits to family and society | 44% | Genetic counseling and testing of other family members is available. |
| Prevention of mortality | No | 15% | Mortality is not a significant component of the condition. [1,2]. |
| Confirmation of diagnosis | Limited availability | 56% | Mat1A mutation analysis; plasma S-adenosylmethionine levels; MAT activity in liver biopsies is now done less frequently since patients are infrequently affected [1,2]. |
| Acute management | Limited availability | 58% | Neurologic and metabolic disease physicians needed [2]. |
| Simplicity of therapy | Periodic involvement of specialist | 45% | Monitoring of methionine and S-adenosylmethionine requires specialist involvement [2]. |

**Hypermethioninemia (MAT I/III Deficiency)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1121 /2100 | % of max score | 53% |
| Rank: | 0.37 %ile | | |
| Observed significant discrepancies with literature | | | |

**ASSESSMENT**

**Secondary target**

**COMMENT**

The great majority of cases of MATI/III deficiency have been ascertained through screening of newborns for cystathionine ß-synthase deficiency. There is limited outcome data available from treated patients. Since the condition is found as by-product of screening for other core panel conditions, those involved in diagnostic confirmation make the programs aware of the diagnosis and follow-up cases as needed.

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| | |
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| CONDITION | Maple syrup (urine) disease |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism |
| ETHNICITY | No ethnic variability though more common in selected population. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 32 of 51 states, 57% of annual births (August 2004) |

| Responses: | 84 | Valid scores: | 1,478 | 97% | PubMed references (August 2004) | 877 |
|---|---|---|---|---|---|---|

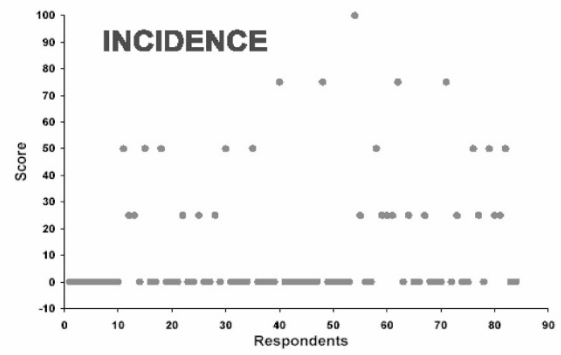
| Gene | *BCKDHA BCKDHB, DBT, DLD* | Locus | *19q13.1-13.2* | OMIM | *608348; 248611; 248610; 248611; 246900* |
|---|---|---|---|---|---|

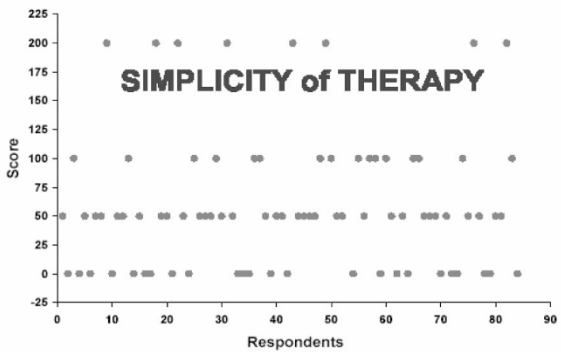
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 15% | 1:230,028 in US newborn screening based on 13,801,657 newborns screened [1]. 1:176 in Old Order Mennonites [2]. |
| Phenotype at birth | <25% of cases | 79% | Nonspecific symptoms at 4-7 days of life; usually affected by 2 yrs [3]. |
| Burden if untreated | Profound | 98% | Coma and death in the more common and severe classic form. Intermittent episodes of metabolic decompensation in intermediate form [3]. |
| The test | | | |
| Screening test | Yes | 98% | BIA available. MS/MS neutral loss scan of m/z 102 for amino acid profiling. Primary markers are ILE/LEU and VAL, first reported in 1995 [4]. |
| Doable in DBS or by physical method | Yes | 100% | Yes, see [4]. |
| High throughput | Yes | 86% | 500-1,000 specimens per day [5]. |
| Overall cost <$1 | <$1/test | 68% | Cost likely higher if only a few conditions are screened [6]. |
| Multiple analytes | Yes | 75% | Leucine/isoleucine (isomers detected together) and valine [4]. |
| Secondary targets | Yes | 62% | E3 deficiency, BCAA transaminase [3]. |
| Multiplex platform | Yes | 68% | For comprehensive review see [5]. |
| The treatment | | | |
| Availability & cost | Limited availability | 62% | Requires metabolic disease specialist and dietician to reduce leucine in diet [8]. Thiamine responsiveness should be assessed. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 52% | Outcome is improved but not fully normalized [3,7]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 90% | Outcome is improved but not fully normalized [3,7]. |
| Benefits of early identification | CLEAR benefits to family and society | 92% | Genetic counseling available [8]. |
| Prevention of mortality | Yes | 93% | Death is common without treatment [3]. |
| Confirmation of diagnosis | Limited availability | 77% | Plasma amino acids, urine organic acids. Alloisoleucine and cellular enzyme diagnosis of BCKD by overall oxidation of 14C-labeled leucine to 14CO2 [3]. Mutation analysis is of limited availability. |
| Acute management | Limited availability | 56% | Well established protocols; metabolic specialist are of limited availability [7]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 30% | Dietary management and frequent monitoring require metabolic disease specialist and dietician [8]. |

**Maple syrup (urine) disease**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1483 /2100 | % of max score | 71% |
| Rank: | 0.89 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Maple syrup (urine) disease had one of the highest scores of the panel of conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel.

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| | |
|---|---|
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| CONDITION | Ornithine transcarbamylase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism (urea cycle disorder) |
| ETHNICITY | Panethnic; no known ethnic differences. |
| SCREENING METHOD(S) | No sensitive and specific test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | 64 |
|---|---|

| Valid scores: | 1,123 | 97% |
|---|---|---|

| PubMed references (August 2004) | 2,384 |
|---|---|

| Gene | *OTC* |
|---|---|

| Locus | *Xp21.1* |
|---|---|

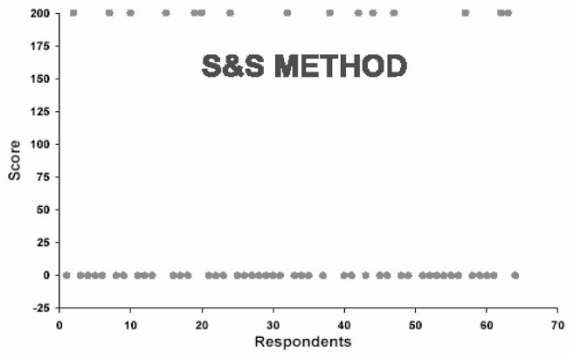
| OMIM | *300461* |
|---|---|

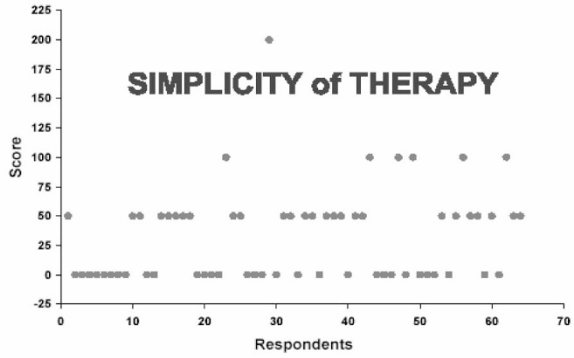
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:75,000 (discrepancy with literature) | 38% | 1:14,000 [1]. |
| Phenotype at birth | <25% of cases | 71% | Early neonatal onset in affected males is relatively common [2,3]. |
| Burden if untreated | Profound | 94% | Developmental delay and mental retardation due to hyperammonemia. Usually lethal in symptomatic male newborns [3,4]. |
| The test | | | |
| Screening test | No | 25% | No, monitoring of low citrulline levels lacks sensitivity and specificity. |
| Doable in DBS or by physical method | No | 31% | No. |
| High throughput | No | 25% | No. |
| Overall cost <$1 | No (>$1/test) | 20% | Not applicable. |
| Multiple analytes | No | 20% | Not applicable. |
| Secondary targets | No | 23% | OTC, CPS and NAGS deficiency have identical biochemical phenotypes by amino acid analysis. Urine orotic acid is elevated in OTC deficiency. |
| Multiplex platform | No | 26% | Not applicable. |
| The treatment | | | |
| Availability & cost | Limited availability | 40% | Protein restricted diet [7,8]; sodium benzoate, sodium phenylacetate or phenylbutyrate [9]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 37% | Natural history with treatment is poorly understood. Mortality improved but morbidity remains significant, particularly in neonatal onset cases [1, 6]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes outcome | 78% | Aggressive treatment may prevent serious morbidity and mortality if it includes liver transplantation [1, 6]. |
| Benefits of early identification | Clear benefits to family and society | 79% | Genetic counseling and prenatal diagnosis are available [3]. |
| Prevention of mortality | Yes | 83% | Yes, with liver transplantation in severe cases [1, 3-5,10]. |
| Confirmation of diagnosis | Limited availability | 53% | Plasma amino acid analysis and urine orotic acid. Liver biopsy for enzyme assay may still be required in cases with inconclusive genotyping. Mutation analysis is available [5]. |
| Acute management | Limited availability | 43% | Requires metabolic specialist and multidisciplinary team [3,5]. |
| Simplicity of therapy | Regular involvement of a specialist | 16% | Metabolic specialists in a multidisciplinary team [3, 5]. |

**Ornithine transcarbamylase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 942 /2100 | % of max score | 45% |
| Rank: | 0.27 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

The amino acid profile by MS/MS cannot detect this condition consistently. There is no objective evidence at this time in support of the availability of a screening test. However, if a newborn is found to have significantly low citrulline, CPS and OTC deficiency are clearly clinically significant conditions and as such should be reported as soon as possible. There is a high false positive rate associated with low citrulline levels due to low protein intake in neonates.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| CONDITION | Phenylketonuria (phenylalanine hydroxylase deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error of metabolism, amino acid disorder |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | BIA, fluorometric, enzyme, tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 51 of 51 states, 100% of annual births (August 2004) |

| Responses: | 120 | Valid scores: | 2,083 | 96% | PubMed references (August 2004): | 5,522 |
|---|---|---|---|---|---|---|

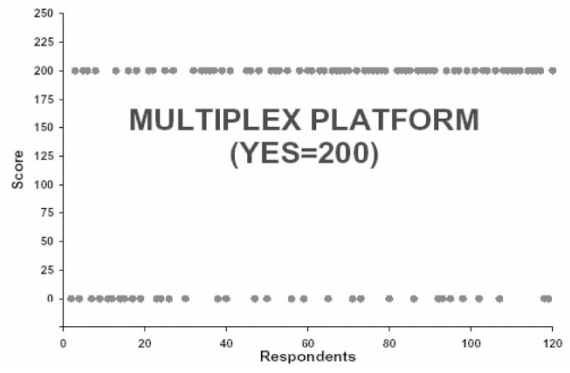
| Gene | *PAH* | Locus | *12q24.1* | OMIM | *261600* |
|---|---|---|---|---|---|

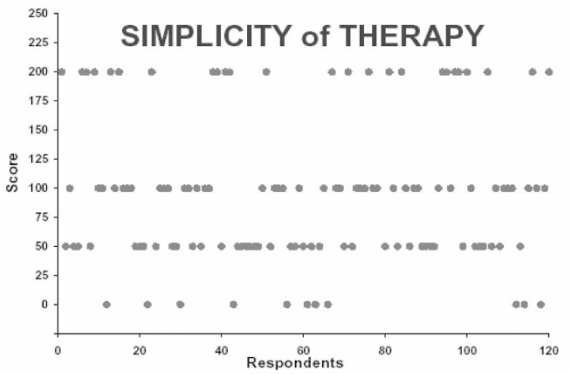
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:25,000 | 79% | 1:19,079 by historical US NBS data [1], highest among Caucasians and Hispanic births. |
| Phenotype at birth | Almost never | 98% | Affected infants usually become apparent by 6 months of age with signs of mental retardation [2]. |
| Burden if untreated | Profound | 95% | Epilepsy (25%), IQs <35 (50%), 36 – 67 (50%), >68 (5%). Microcephaly, delayed or absent speech and behavioral abnormalities are common features [3]. |
| The test | | | |
| Screening test | Yes | 99% | BIA available since 1963 [4]. MS/MS neutral loss scan of m/z 102 for amino acid profiling. Primary marker is PHE [5]. |
| Doable in DBS or by physical method | Yes | 99% | BIA and MS/MS doable in dried blood spots [4,5]. |
| High throughput | Yes | 89% | Up to 500 - 1,000 specimens per day [6]. |
| Overall cost <$1 | Yes | 70% | Cost likely higher if MS/MS is used to screen for 1 - 3 conditions only (CT, MI, NY, RI, VA, WA) [7]. |
| Multiple analytes | Yes | 71% | PHE, TYR, PHE/TYR ratio [5]. |
| Secondary targets | Yes | 70% | Biopterin cofactor biosynthesis and regeneration defects [8]. |
| Multiplex platform | Yes (lack of consensus) (*) | 68% | For comprehensive review see [9]. |
| The treatment | | | |
| Availability & cost | Limited availability, relatively expensive | 79% | Medical foods for PKU are generally available and relatively expensive, though cost effective [10]. |
| Efficacy of treatment | Potential to prevent ALL negative consequences | 72% | Normalization of phe and tyr in blood prevents cognitive deficits that are attributable to PKU [11,12]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 97% | Normalization of phe and tyr in blood prevents cognitive deficits that are attributable to PKU [11,12]. |
| Benefits of early identification | CLEAR evidence of benefits to family & society | 99% | Genetic counseling and prenatal diagnosis available [13]. |
| Prevention of mortality | No | 31% | Significant morbidity if untreated but no early increase in mortality [3]. |
| Confirmation of diagnosis | Widely available | 90% | Diagnostic tests for PKU are to distinguish benign hyperphenylalaninemia from clinically significant forms [3]. Molecular testing is available [14]. |
| Acute management | Limited availability | 78% | Well established protocols [3]. |
| Simplicity of therapy | Periodic involvement of specialist (lack of consensus) (*) | 47% | Maintenance of Phe levels in the range of 1-6 mg/dL [2, 11]. |

**Phenylketonuria (phenylalanine hydroxylase deficiency)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | YES | Type | MS/MS, others |
| 2ary target of higher scoring condition? | | | NO |
| Final score | 1663 /2100 | % of max score | 79% |
| Rank: | 98 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

PKU had the third highest score of the panel of conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel. Differential diagnosis of secondary targets needs to be considered.

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| | |
|---|---|
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| 14 | Kayaalp E et al. Human phenylalanine hydroxylase mutations and hyperphenylalaninemia phenotypes. Am J Hum Genet 1997;61:1309-20. |

| CONDITION | Tyrosinemia type I (hepatorenal tyrosinemia) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism |
| ETHNICITY | Highest in French Canadian (Quebec) at 1:12,500 [1]; 1:100,000 in Northern Europe [2]. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 21 of 51 states, 30% of annual births (August 2004) |

| Responses: | 68 |
|---|---|

| Valid scores: | 1,183 | 97% |
|---|---|---|

| PubMed references (August 2004) | 150 |
|---|---|

| Gene | *FAH* |
|---|---|

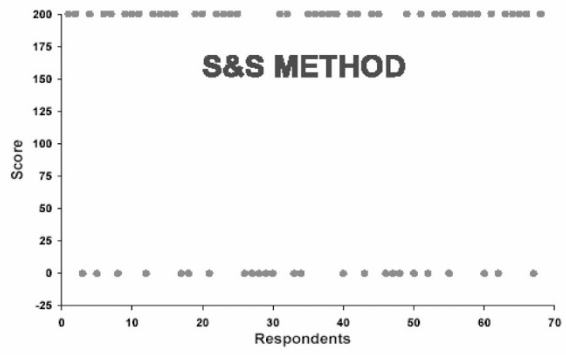
| Locus | *15Q23-Q25* |
|---|---|

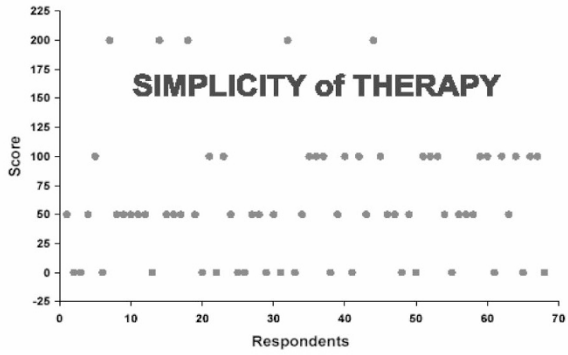
| OMIM | *276700* |
|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 9% | 1:100,000 - 1:120,000 in Northern Europe (Scandinavia) [2]. |
| Phenotype at birth | Almost never | 84% | Liver failure in infancy in acute form (most of those with Type 1) but rarely prior to screening [3]. |
| Burden if untreated | Profound | 93% | Protracted course of liver disease and bleeding as well as hepatocellular carcinoma and death in acute and chronic forms [3, 4]. |
| The test | | | |
| Screening test | Yes | 63% | MS/MS [5]. However, the majority of cases are likely missed. Screening by succinylacetone in Quebec proved to be sensitive and specific but was not high throughput [3,6]. |
| Doable in DBS or by physical method | Yes | 82% | Yes, see [5,6]. |
| High throughput | Yes | 70% | Up to 500 - 1,000 specimens per day [5]. |
| Overall cost <$1 | No (>$1/test ) | 48% | Cost likely higher if MS/MS is used to screen for 1 - 3 conditions only (CT, MI, NY, RI, VA, WA) [7]. |
| Multiple analytes | Yes | 52% | Tyrosine, succiniylacetone, methionine [5]. |
| Secondary targets | Yes | 50% | Yes, see [5]. |
| Multiplex platform | Yes | 50% | Yes, see [5]. |
| The treatment | | | |
| Availability & cost | Limited availability | 44% | Metabolic physicians are of limited availability; NTBC markedly reduces risk of hepatic or neurologic decompensation [4]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 49% | NTBC is of clear short-term benefit in management of acute crises. Data are limited on long-term benefits and risks [8,9]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes outcome | 79% | NTBC has greatly improved survival of patients with acute tyrosinemia and has reduced need for liver transplants in early childhood [8-11]. |
| Benefits of early identification | CLEAR benefits to family and society | 85% | Genetic counseling and prenatal diagnosis available. Molecular testing available [4]. |
| Prevention of mortality | Yes | 90% | NTBC is of clear short-term benefit in management of acute crises. Data are limited on long-term benefits and risks [8-11]. |
| Confirmation of diagnosis | Limited availability | 64% | Hypertyrosinemia and abnormal urinary levels of tyrosine metabolites requires metabolic disease physician involvement. [4,11,12] Fumarylacetoacetase hydroxylase activity can be measured. |
| Acute management | Limited availability | 54% | Dietary management and NTBC treatment require involvement of metabolic disease physicians, who are of limited availability [4]. |
| Simplicity of therapy | Regular involvement of specialist | 30% | Dietary management and NTBC treatment require involvement of metabolic disease physicians, who are of limited availability [4]. |

**Tyrosinemia type I (hepatorenal tyrosinemia)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1257 /2100 | % of max score | 60% |
| Rank: | 0,64 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Transient tyrosinemia of the newborn is the most common amino acid disorder in humans. Metabolic disease physicians are valuable in discriminating among causes of hypertyrosinemia and in dietary management. Newborn screening is based on the detection of an elevated concentration of tyrosine. Elevated methionine may also be present. There is evidence of lower sensitivity with the current testing technology (affected cases with normal concentration when tested at birth and poor specificity (high rate of false positive results, mostly premature babies and newborns with liver disease of variable etiology). Tyrosinemia type I is included in our core panel for both historical reasons and because detection by elevated methionine justifies inclusion. Further, it is a severe condition for which an efficacious treatment (NTBC) is available. It remains important that the diagnosis of tyrosinemia not be presumed to have been excluded on the basis of a screen negative result.

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| | |
|---|---|
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| CONDITION | Tyrosinemia type II (oculocutaneous tyrosinemia) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism |
| ETHNICITY | No known ethnic differences. Half of reported cases are of Italian descent. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 17 of 51 states, 25% of annual births (August 2004) |

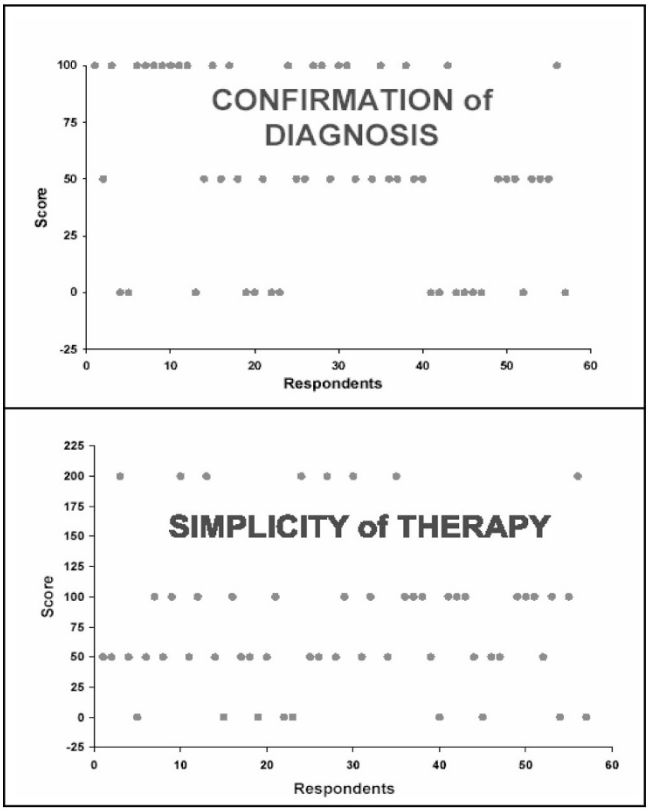
| Responses: | 57 | Valid scores: | 975 | 95% | PubMed references (August 2004) | 95 |
|---|---|---|---|---|---|---|

| Gene | *TAT* | Locus | *16q22.1-q22.3* | OMIM | *276600* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 5% | Not known (case reports). |
| Phenotype at birth | Almost never | 93% | Variable age of onset. Ocular manifestation may rarely appear at birth. Skin finding usually seen after first year of life [1]. |
| Burden if untreated | Moderate | 64% | Ophthalmologic and skin findings in most. Variable levels of mental retardation [2-5]. |
| The test | | | |
| Screening test | Yes | 75% | MS/MS [6]. |
| Doable in DBS or by physical method | Yes | 93% | Yes, see [6]. |
| High throughput | Yes | 80% | Up to 500 - 1,000 specimens per day [6]. |
| Overall cost <$1 | <$1/test | 60% | Cost likely higher if MS/MS is used to screen for 1 - 3 conditions only (CT, MI, NY, RI, VA, WA) [7]. |
| Multiple analytes | Yes | 62% | Tyrosine. |
| Secondary targets | Yes | 56% | Yes, see [6]. |
| Multiplex platform | Yes | 67% | Yes, see [6]. |
| The treatment | | | |
| Availability & cost | Limited availability | 69% | Dietary management of tyrosine and phenylalanine levels requires a metabolic disease physician [3]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 59% | Eye and skin lesions resolve after a few weeks [3, 8]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes outcome | 54% | Eye and skin lesions resolve after a few weeks [3, 8]. |
| Benefits of early identification | SOME benefits to family and society | 71% | Genetic counseling is available. |
| Prevention of mortality | No | 25% | Reduced mortality is not a significant component of condition. |
| Confirmation of diagnosis | Limited availability | 55% | Hypertyrosinemia and abnormal urinary levels of tyrosine metabolites with normal phenylalanine require metabolic disease physician involvement [4]. |
| Acute management | Limited availability | 55% | Dietary management of tyrosine and phenylalanine levels require a metabolic disease physician [3] |
| Simplicity of therapy | Periodic involvement of specialist | 40% | Dietary management of tyrosine and phenylalanine levels and monitoring require a metabolic disease physician [3]. |

**Tyrosinemia type II (oculocutaneous tyrosinemia)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1249 /2100 | % of max score | 59% |
| Rank: | 0.61 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Transient tyrosinemia of the newborn is the most common amino acid disorder in humans. Metabolic disease physicians are valuable in discriminating among causes of hypertyrosinemia and in dietary management. Newborn screening is based on the detection of an elevated concentration of tyrosine. Elevated methionine may also be present. There is evidence of lower sensitivity with the current testing technology (affected cases with normal concentration when tested at birth) and poor specificity (high rate of false positive results, mostly premature babies and newborns with liver disease of variable etiology).

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| CONDITION | Tyrosinemia type III (4-hydroxyphenylpyruvate dioxygenase def.) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of amino acid metabolism |
| ETHNICITY | No known ethnic differences. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | 42 | Valid scores: | 724 | 96% | PubMed references (August 2004) | 189 |
|---|---|---|---|---|---|---|

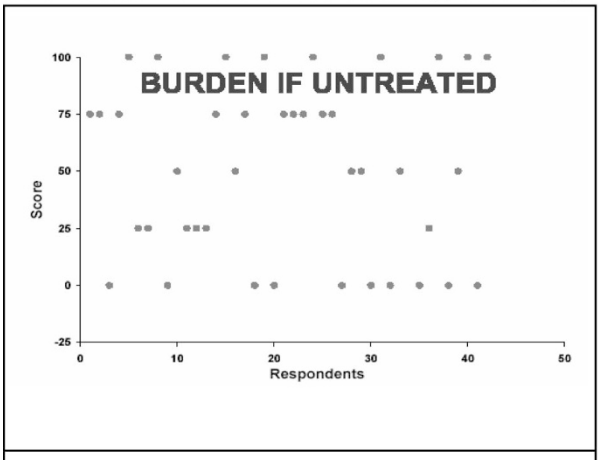
| Gene | *HPD* | Locus | *12q24-qter* | OMIM | *276710* |
|---|---|---|---|---|---|

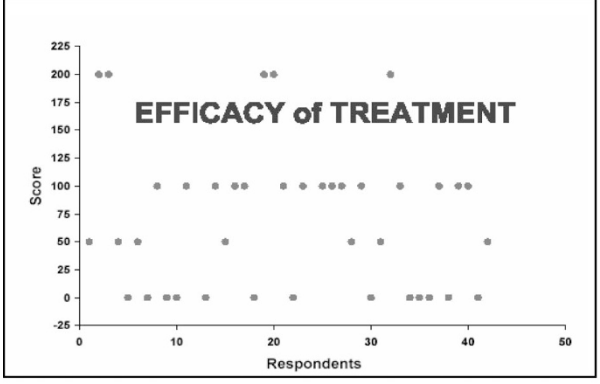
| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | <1:100,000 | 7% | Not known (case reports). |
| Phenotype at birth | Almost never | 86% | Rarely [1,2]. |
| Burden if untreated | Moderate | 51% | Metabolic acidosis and failure to thrive in infancy. Neurologic abnormalities in most. Mental retardation in >50% [1-4]. |
| The test | | | |
| Screening test | Yes | 76% | MS/MS [5]. |
| Doable in DBS or by physical method | Yes | 93% | Yes, see [5]. |
| High throughput | Yes | 78% | Up to 500 - 1,000 specimens per day [5]. |
| Overall cost <$1 | <$1/test | 60% | Cost likely higher if MS/MS is used to screen for 1 - 3 conditions only (CT, MI, NY, RI, VA, WA) [6]. |
| Multiple analytes | Yes | 62% | Tyrosine [5]. |
| Secondary targets | Yes | 54% | Yes, see [5]. |
| Multiplex platform | Yes | 66% | Yes, see [5]. |
| The treatment | | | |
| Availability & cost | Limited availability | 73% | Dietary management of tyrosine and phenylalanine levels requires a metabolic disease physician [7,8]. |
| Efficacy | Potential to prevent SOME negative consequences | 36% | Limited experience. Tyrosine restriction seems to improve behavioral problems, though not mental retardation (see comment) [7,8]. |
| Early intervention | SOME evidence that early intervention optimizes individual outcome | 41% | Limited experience. Tyrosine restriction seems to improve behavioral problems, though not mental retardation (see comment) [7,8]. |
| Early identification | SOME benefits to family and society | 54% | Genetic counseling is available [2]. |
| Mortality prevention | No | 26% | Not a significant component of the condition [2]. |
| Diagn. confirmation | Limited availability | 54% | Metabolic disease physicians needed for the discrimination between type 1 and other types [2]. |
| Acute management | Limited availability | 59% | Reduction of tyrosine with low protein diet [2]. |
| Simplicity of therapy | Periodic involvement of specialist | 42% | Metabolic disease physicians are needed periodically for monitoring [2]. |

**Tyrosinemia type III**

**(4-hydroxyphenylpyruvate dioxygenase def.)**

CRITERIA OF LEAST CONSENSUS see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1149 /2100 | % of max score | 55% |
| Rank: | 0.47 %ile | | |

**ASSESSMENT**

**Secondary target, report only**

**COMMENT**

Few cases are reported. It is likely that the condition is relatively benign. There is evidence of ascertainment bias for patients previously reported with mental retardation. Transient tyrosinemia of the newborn is the most common amino acid disorder in humans. Metabolic disease physicians are valuable in discriminating among causes of hypertyrosinemia and in dietary management. Newborn screening is based on the detection of an elevated concentration of tyrosine. Elevated methionine may also be present. There is evidence of lower sensitivity with the current testing technology (affected cases with normal concentration when tested at birth) and poor specificity (high rate of false positive results, mostly premature babies and newborns with liver disease of variable etiology).

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| | |
|---|---|
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| 3 | Giardini O et al. Chronic tyrosinemia associated with 4-hydroxyphenylpyruvate dioxygenase deficiency with acute intermittent ataxia and without visceral and bone involvement. Pediat Res 1983;17:25-29. |
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# FATTY ACID OXIDATION DEFECTS

| CONDITION | Carnitine: acylcarnitine translocase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | No known population at increased risk. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 18 of 51 states, 28% of annual births (August 2004) |

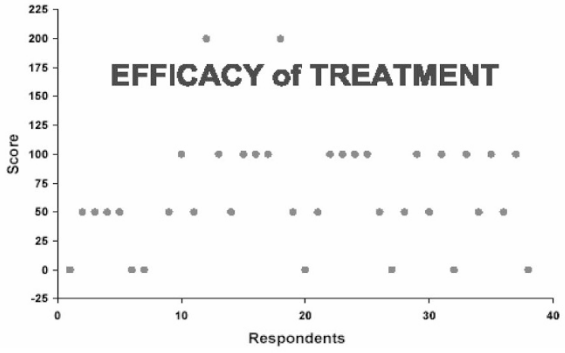
| Responses: | 38 | Valid scores: | 643 | 94% | PubMed references (August 2004) | 1,726 |
|---|---|---|---|---|---|---|

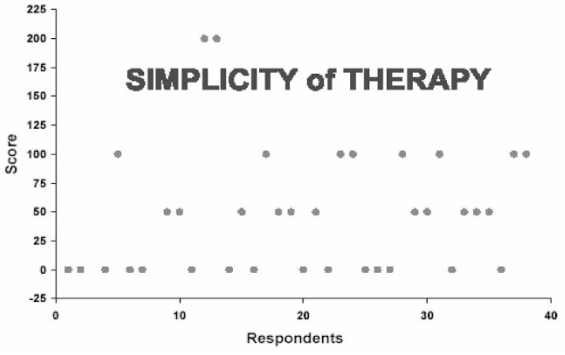
| Gene | *CACT* | Locus | *3p21.31* | OMIM | *212138* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | <1:100,000 | 10% | First reported in 1992 [1], approximately 30-50 cases described worldwide, likely underdiagnosed. |
| Phenotype at birth | <25% of cases | 68% | Multiple reports of severe neonatal decompensation (hypoglycemia, hyperammonemia) and sudden unexpected death in newborns [2]. |
| Burden if untreated | Profound | 91% | Mortality is 30-50% at first episode [3]. Milder cases (with higher residual enzyme activity) have been reported [4]. |
| The test | | | |
| Screening test | Yes | 74% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary markers are C16-C18 species [5]. |
| Doable in DBS or by physical method | Yes | 83% | See [6]. |
| High throughput | Yes | 74% | Up to 500-1,000 specimens per day [6]. |
| Overall cost <$1 | No (>$1/test) | 41% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [7]. |
| Multiple analytes | Yes | 74% | C16-C18 saturated and unsaturated acylcarnitines [6]. |
| Secondary targets | Yes | 58% | Differential diagnosis with CPT II deficiency [8]. |
| Multiplex platform | Yes | 62% | For comprehensive review see [6]. |
| The treatment | | | |
| Availability & cost | Limited availability | 57% | Avoidance of fasting, MCT oil supplementation, night time corn starch. Conjugating agents for hyperammonemia [3,8,9,10,11]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (lack of consensus) (*) | 34% | Early diagnosis and treatment may not prevent mortality due to arrhythmias [3,9,11]. No long-term data available. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 55% | Some prevention of mortality [3,8,9,10,11]. |
| Benefits of early identification | SOME benefits to family and society | 68% | Genetic counseling, retrospective diagnoses of sudden death cases, prevention of costs for care of episodes [3,8,9,11]. |
| Prevention of mortality | Yes | 68% | Prevention of sudden and unexpected death is hindered by life-threatening episodes of arrhythmias [3,9]. |
| Confirmation of diagnosis | Only a few centers | 28% | Plasma acylcarnitines and urine organic acid analysis [11,12,13]; enzyme assay; genotyping available only in a few laboratories [10,14]. |
| Acute management | Limited availability | 45% | Standard emergency protocols for long-chain fatty acid oxidation disorders are effective [3,8,9,10,11]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 24% | No special food or orphan drug required [3,8,9,10,11]. |

**Carnitine: acylcarnitine translocase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1141 /2100 | % of max score | 54% |
| Rank: | 0.43 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

The incidence and natural history of CACT deficiency are poorly understood. Avoidance of fasting and dietary treatment do not seem to prevent mortality due to unpredictable episodes of arrhythmia. Specificity and sensitivity of NBS by acylcarnitine profiling are undetermined. For these reasons, CACT is not recommended for inclusion in the uniform panel. However, a profile suggestive of a possible diagnosis of CACT deficiency is clinically significant and should be reported when detected.

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| CONDITION | Carnitine palmitoyltransferase I deficiency (CPT-1a) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | Founder effect in North American Hutterites. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS), DNA-based in selected population |
| NBS STATUS in the US | Screened for in 11 of 51 states, 13% of annual births (August 2004) |

| Responses: | 40 | Valid scores: | 690 | 96% | PubMed references (August 2004) | 8,278 |
|---|---|---|---|---|---|---|

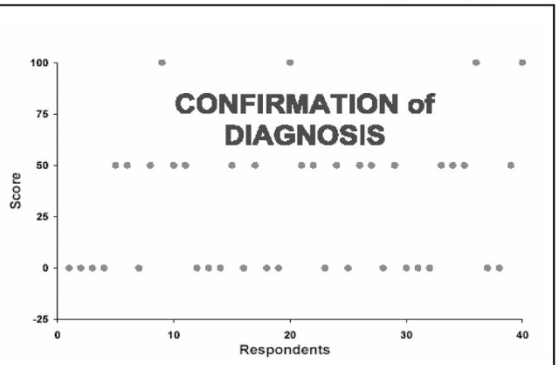
| Gene | *CPT1A* | Locus | *11q13* | OMIM | *600528* |
|---|---|---|---|---|---|

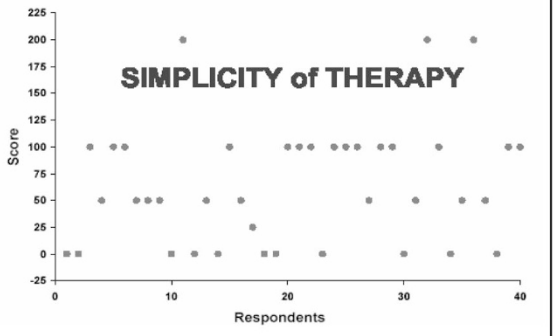
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 10% | First reported in 1981 [1], anecdotal reports worldwide with diverse ethnicity. 1:1,200 births in Hutterites [2]. |
| Phenotype at birth | <25% of cases | 75% | Neonatal onset of hypoketotic hypoglycemia, convulsions, coma, renal tubular acidosis, and Reye-like episodes has been reported [3,4]. |
| Burden if untreated | Profound | 89% | Acute episodes are life-threatening [3,4,5]; tendency to decreased frequency and severity of attacks with time and fasting avoidance. Maternal complications could be severe (AFLP) [6]. |
| The test | | | |
| Screening test | Yes (MS/MS) | 53% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary markers is calculation of [C0/(C16+C18)] ratio [7]. |
| Doable in DBS or by physical method | Yes | 67% | See [7,8]. |
| High throughput | Yes | 58% | Up to 500-1,000 specimens per day [8]. |
| Overall cost <$1 | No (>$1/test) | 44% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [9]. |
| Multiple analytes | Yes | 56% | Free carnitine (elevated), C16 and C18 (low) [7]. |
| Secondary targets | No | 41% | CPT Ib deficiency, although confirmed cases have not been reported to date [10]. |
| Multiplex platform | Yes | 54% | For comprehensive review see [8]. |
| The treatment | | | |
| Availability & cost | Limited availability | 64% | Avoidance of fasting, MCT oil supplementation, aggressive treatment of intercurrent illnesses [3,4,10,11,16]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 46% | Cases diagnosed by NBS may remain asymptomatic with avoidance of fasting [7]. No long-term data available [16]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 62% | Expectation of normal growth and development. Prevention of mortality [3,4,10,11]. |
| Benefits of early identification | SOME benefits to family and society | 69% | Retrospective diagnosis of sudden death cases [7], prevention of costs for care of episodes [4]. |
| Prevention of mortality | Yes | 82% | Prevention of sudden and unexpected death [3,4,10,11]. |
| Confirmation of diagnosis | Only a few centers (lack of consensus) (*) | 31% | Plasma carnitine and acylcarnitines [12,13]; chances of being overlooked if work-up is limited to plasma acylcarnitines and urine organic acids (negative); enzymology and genotyping available only in a few laboratories [14-16]. |
| Acute management | Limited availability | 51% | Standard emergency protocols for long-chain fatty acid oxidation disorders are effective [3,4,10,11]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 33% | No special food or orphan drug required [3,4,10,11]. |

**Carnitine palmitoyltransferase I deficiency (CPT-1a)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1131 /2100 | % of max score | 54% |
| Rank: | 0.40 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

The incidence and natural history of CPT I deficiency are not well ascertained outside a small ethnic group. The sensitivity and specificity of the ratio used as a primary screen are also unknown and could represent an interpretive challenge to less experienced laboratories. For these reasons, CPT I deficiency is not recommended for inclusion in the uniform panel. However, a profile suggestive of a possible diagnosis of CPT I deficiency is clinically significant and should be reported when detected.

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| CONDITION | Carnitine palmitoyltransferase II deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | No known population at increased risk. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

| Responses: | 45 | Valid scores: | 772 | 95% | PubMed references (August 2004) | 2067 |
|---|---|---|---|---|---|---|

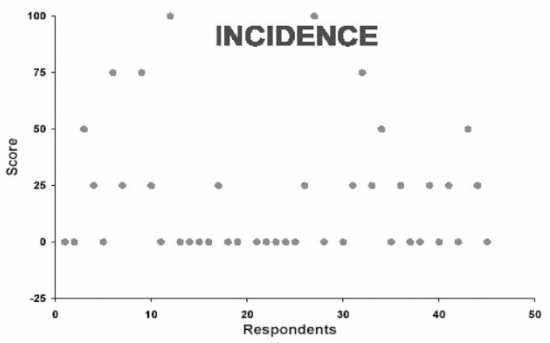
| Gene | *CPT2* | Locus | 1p32 | OMIM | *600650* |
|---|---|---|---|---|---|

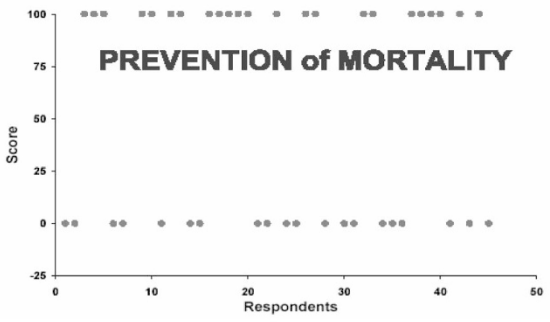
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 20% | First reported in 1973 [1], >200 cases described worldwide; lack of consensus reflects clinical impression of a relatively common disorder [2]. |
| Phenotype at birth | <25% of cases | 67% | <20 cases reported with the severe, usually lethal, neonatal presentation associated with congenital anomalies [2,3]. |
| Burden if untreated | Severe | 76% | Episodes of muscle pain and weakness are transient. Life-threatening complications include renal failure due to rhabdomyolysis with massive myoglobinuria and respiratory insufficiency [4-6]. |
| The test | | | |
| Screening test | Yes | 78% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary markers are C16-C18 species. First prospectively diagnosed case was reported in 2001 [7,8]. |
| Doable in DBS or by physical method | Yes | 84% | See [7]. |
| High throughput | Yes | 74% | Up to 500-1,000 specimens per day [9]. |
| Overall cost <$1 | No (>$1/test) | 49% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [10]. |
| Multiple analytes | Yes | 73% | C16-C18 saturated and unsaturated acylcarnitines [9]. |
| Secondary targets | No | 55% | Differential diagnosis with CACT deficiency [11]. |
| Multiplex platform | Yes | 68% | For comprehensive review see [9]. |
| The treatment | | | |
| Availability & cost | Limited availability | 72% | Avoidance of fasting, prolonged exercise, cold exposure, and other stressors [6]; bezafibrate is effective in vitro [12]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 41% | Treatment is usually effective to prevent acute episodes [6]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 44% | Some prevention of mortality [4,6,12,13]. |
| Benefits of early identification | SOME benefits to family and society | 63% | Genetic counseling, prevention of costs for care of episodes [6]. |
| Prevention of mortality | Yes (lack of consensus) (*) | 53% | CPT II deficiency is not a significant cause of mortality, early onset cases are usually lethal despite treatment [5,6,13]. |
| Confirmation of diagnosis | Only a few centers | 36% | Plasma acylcarnitines [3,4]; genotyping available only in a few laboratories [6,15,17,18]; enzyme assay [15,17]. |
| Acute management | Limited availability | 48% | Standard emergency protocols for long-chain fatty acid oxidation disorders are effective [4,6,13]. |
| Simplicity of therapy | Regular involvement of specialist | 31% | No special food required [4,6], and experimental drug (bezafibrate) is under investigation [12]. |

**Carnitine palmitoyltransferase II deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1169 /2100 | % of max score | 56% |
| Rank: | 0.51 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

The natural history of CPT II deficiency is well understood, incidence remains uncertain. The sensitivity and specificity of long-chain acylcarnitine species used as primary screening are also unknown and could represent an interpretive challenge to less experienced laboratories. Treatment, however, by avoidance of fasting and other stressors is effective. For these reasons, M/SCHAD is not recommended for inclusion in the uniform panel. However, a profile suggestive of a possible diagnosis of M/SCHAD is clinically significant and should be reported when detected.

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| | |
|---|---|
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| 10 | National Newborn Screening & Genetics Resource Center: Current newborn conditions by state (as of 07-05-04), http://genes-r-us.uthscsa.edu/. |
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| CONDITION | Carnitine uptake deficiency (systemic) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

| Responses: | 46 | Valid scores: | 810 | 98% |
|---|---|---|---|---|

| PubMed references (August 2004) | 171 |
|---|---|

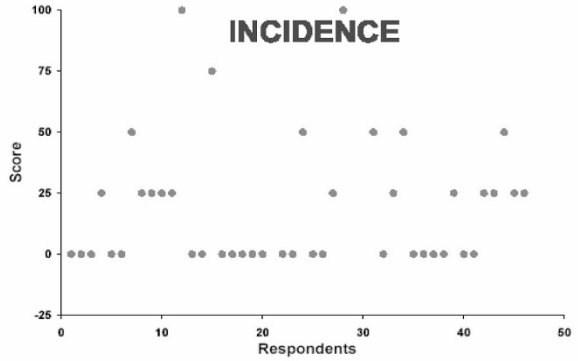
| Gene | *SLC22A5* | Locus | *5q33.1* | OMIM | *212140* |
|---|---|---|---|---|---|

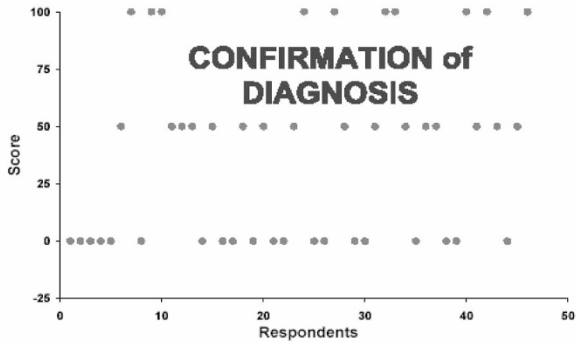
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 19% | Inherited defect in membrane transport was first reported in 1988 [1]. Incidence is not known; 1:40,000 in Japan [2]. |
| Phenotype at birth | Almost never | 82% | 50% of reported cases presented between age 3 months and 2.5 yrs. with metabolic decompensation including cardiomyopathy in some. Others present later with cardiomyopathy [3,4]. |
| Burden if untreated | Profound | 88% | Hypoketotic hypoglycemia, hyperammonemia, cardiomyopathy in some progressing to coma and death. Sudden infant death has been observed [3-7]. |
| The test | | | |
| Screening test | Yes | 55% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary marker is free carnitine. Anecdotal observations of possible low sensitivity when done in the first 24 hrs [8,9]. |
| Doable in DBS or by physical method | Yes | 64% | Yes [8,9]. |
| High throughput | Yes | 51% | Up to 500-1,000 specimens per day [8]. |
| Overall cost <$1 | No (>$1/test) | 36% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [10]. |
| Multiple analytes | No | 42% | Free carnitine, low acylcarnitine levels. |
| Secondary targets | No | 39% | Severe nutritional deficiency [8,9]. |
| Multiplex platform | Yes | 48% | For comprehensive review see [8]. |
| The treatment | | | |
| Availability & cost | Widely available | 82% | Carnitine, avoidance of fasting [4,11-14,17]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 68% | Cases diagnosed by NBS may remain asymptomatic with carnitine supplementation [2]. Treatment is effective in preventing episodes but long-term data is lacking [4,11-14,17]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 70% | Expectation of normal growth and development. Prevention of mortality [4,12-14,17]. |
| Benefits of early identification | CLEAR benefits to family and society | 78% | Genetic counseling, prenatal diagnosis, prevention of costs for care of episodes [4,5,12]. |
| Prevention of mortality | Yes | 87% | Prevention of sudden and unexpected death [4,15]. |
| Confirmation of diagnosis | Only a few centers (lack of consensus) (*) | 39% | Carnitine uptake assay and genotyping are of limited availability [16]. |
| Acute management | Limited availability | 70% | Standard emergency protocols for long-chain fatty acid oxidation disorders are effective [4,11,12]. |
| Simplicity of therapy | Regular involvement of specialist | 68% | No special foods or orphan drugs are required [4,11,12]. |

**Carnitine uptake deficiency (systemic)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1309 /2100 | % of max score | 62% |
| Rank: | 0.71 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

There are two forms of CUD. The first presents neonatally with severe metabolic decompensation and sudden infant death. The second form presents later with cardiomyopathy and muscle weakness. Phenotypes are quite variable, but treatment is effective. This condition clearly meets the criteria for inclusion in the uniform panel and state programs should be encouraged to add this condition to their NBS panel.

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| | |
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| CONDITION | Dienoyl-CoA reductase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | One case in an African-American is described. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 2 of 51 states, 4% of annual births (August 2004) |

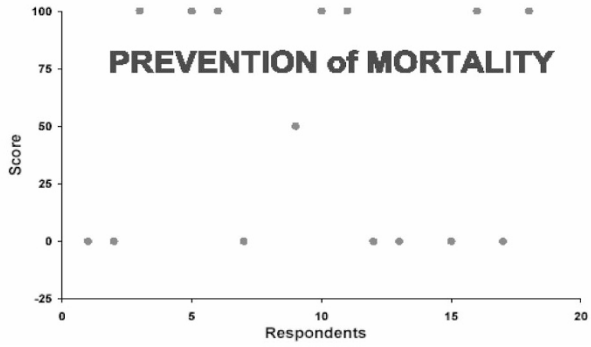
| Responses: | 18 | Valid scores: | 289 | 89% | PubMed references (August 2004) | 9 |
|---|---|---|---|---|---|---|

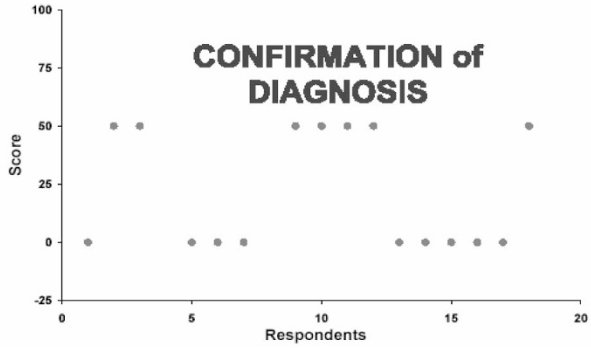
| Gene | *1-Dec* | Locus | *8q21.3* | OMIM | *222745* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | **LITERATURE AND WEB-BASED EVIDENCE** [References] |
| The condition | | | |
| Incidence | <1:100,000 | 8% | Only one case has been described [1,2]. Incidence not known. |
| Phenotype at birth | Almost never | 81% | Hypotonia, small VSD, short extremities and microcephaly at birth though the relationship of phenotype to the disorder is not known [1]. |
| Burden if untreated | Profound | 84% | Patient became septic. Unresponsive respiratory acidosis led to demise [1,2]. |
| The test | | | |
| Screening test | Yes | 77% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary marker is C10:2 (2-trans,4-cis-C10:2) [1]. |
| Doable in DBS or by physical method | Yes | 82% | Yes [1,3]. |
| High throughput | Yes | 76% | Up to 500-1,000 specimens per day [3]. |
| Overall cost <$1 | <$1/test | 53% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [4]. |
| Multiple analytes | Yes | 65% | No [1]. |
| Secondary targets | Yes | 56% | No. |
| Multiplex platform | Yes | 72% | Yes, see [3] for comprehensive review. |
| The treatment | | | |
| Availability & cost | Limited availability | 69% | Not known [2]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 27% | Not known. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 43% | Not known. |
| Benefits of early identification | SOME benefits to family and society | 57% | Not known. |
| Prevention of mortality | No (*) | 50% | Not known. |
| Confirmation of diagnosis (*) | Only a few centers | 22% | Gene is cloned [5] but original patient has not been studied at molecular level. Confirmatory MS/MS is available in fewer than 20 laboratories [6]. |
| Acute management | Limited availability | 44% | Metabolic physicians are of limited availability. |
| Simplicity of therapy | Regular involvement of specialist | 29% | Routine involvement of metabolic physicians is expected [2]. |

**Dienoyl-CoA reductase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1119 /2100 | % of max score | 53% |
| Rank: | 0.36 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

A single patient has been described with this condition [1]. Questions remain as to whether the anomalies noted are coincidental or disease associated. The sensitivity and specificity of the primary marker are also unknown and could represent an interpretive challenge to less experienced laboratories. For these reasons, dienol-CoA-reductase deficiency (DERED) is not recommended for inclusion in the uniform panel. However, a profile suggestive of a possible diagnosis of DERED deficiency is clinically significant and should be reported when detected.

**REFERENCES AND WEB SITES**


| | |
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| 3 | Chace DH et al. Use of tandem mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem 2003;49:1797-1817. |
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| CONDITION | Glutaric acidemia type II |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid and amino acid metabolism |
| ETHNICITY | No known ethnic variability. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 20 of 51 states, 32% of annual births (August 2004) |

| Responses: | 52 | Valid scores: | 899 | 96% | PubMed references (August 2004) | 519 |
|---|---|---|---|---|---|---|

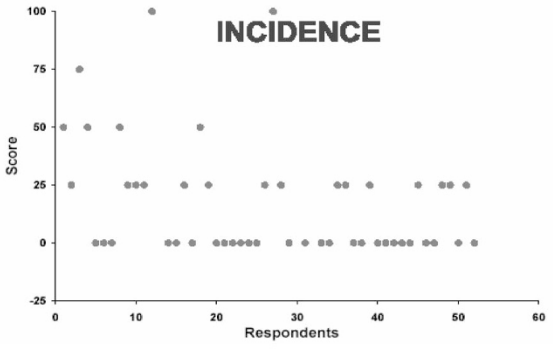
| Gene | ETFA ATFB ETFDH | Locus | 15q23-q25 19q13.3 4q32-qter | OMIM | 231680; 130410; 231675 |
|---|---|---|---|---|---|

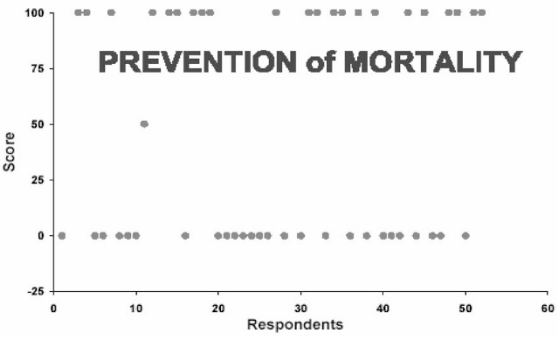
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 17% | Unknown but relatively rare. In 300,000 newborn screens in Wisconsin, 1 severe neonatal case and 1 mild case were detected [1-3]. |
| Phenotype at birth | <25% of cases | 70% | Three forms: 1) neonatal with congenital anomalies that presents in first 24-48 hrs; 2) neonatal without congenital anomalies (rare) that is less apparent at birth; 3) a milder late-onset form [1-3]. |
| Burden if untreated | Profound | 94% | The neonatal forms are generally lethal in the first week of life. The late-onset form is quite variable in its course with episodes of hypoketotic hypoglycemia and hepatic dysfunction but asymptomatic cases are known [1-8]. |
| The test | | | |
| Screening test | Yes | 94% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. C4-C18 species are primary markers [9,10]. |
| Doable in DBS or by physical method | Yes | 94% | See [10]. |
| High throughput | Yes | 85% | Up to 500-1,000 specimens per day [10]. |
| Overall cost <$1 | No (>$1/test) | 54% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [11]. |
| Multiple analytes | Yes | 88% | C4-C18 species, including C5-DC [10]. |
| Secondary targets | Yes | 68% | MCAD [10]. |
| Multiplex platform | Yes | 78% | For comprehensive review see [10]. |
| The treatment | | | |
| Availability & cost | Limited availability | 57% | Dietary management and monitoring and specialized treatments require involvement of a metabolic specialist [1]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 29% | Infant onset form has not been successfully treated. Low protein and fat diets with carnitine supplementation and riboflavin treatment have been more successful in the late onset and milder forms [1,12-14]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 52% | Low protein and fat diets with carnitine supplementation and riboflavin treatment have been more successful in the late-onset and milder forms [1,12-15]. |
| Benefits of early identification | SOME benefits to family and society | 67% | Genetic counseling and prenatal diagnosis are available [16,17]. |
| Prevention of mortality | Yes (lack of consensus) (*) | 46% | Lethality is high in neonatal severe forms and may be reduced in the rare riboflavin responsive forms [1,18]. |
| Confirmation of diagnosis | Only a few centers | 38% | Urinary organic acids reveal characteristic pattern in infantile onset form [1,9]. Late-onset form may only show characteristic patterns during metabolic episodes [1,6,9]. Enzyme diagnosis is difficult and not widely available, and involvement of three different genes complicates molecular diagnostics [1,19]. |
| Acute management | Limited availability | 44% | Management of metabolic crisis requires metabolic specialists that are not widely available [1-9]. |
| Simplicity of therapy | Regular involvement of specialist | 23% | Supportive care, treatments and monitoring are complex and require involvement of specialists [1-9, 16,18]. |

**Glutaric acidemia type II**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1224 /2100 | % of max score | 58% |
| Rank: | 0.59 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

The natural history of GA2 is poorly understood. Treatment options are similar to other FAO disorders with variable outcome. Furthermore, specificity and sensitivity of acylcarnitine profiling are undetermined. For these reasons, GA2 is not recommended for inclusion in the uniform panel. However, a profile suggestive of a possible diagnosis of GA2 is clinically significant and should be reported when detected.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| CONDITION | Long-chain 3-OH acyl-CoA dehydrogenase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 33% of annual births (August 2004) |

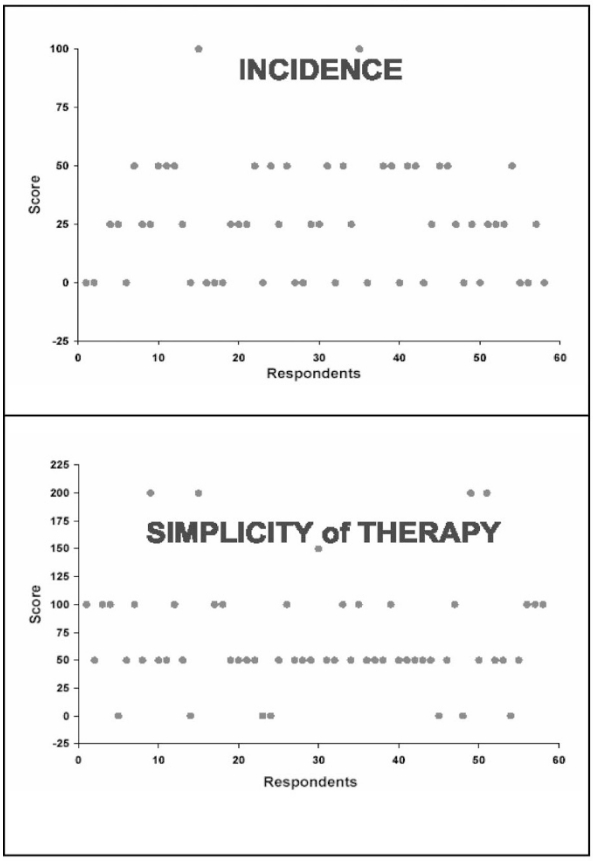
| Responses: | 58 | Valid scores: | 1,015 | 97% | PubMed references (August 2004) | 52 |
|---|---|---|---|---|---|---|

| Gene | *HADHA* | Locus | *2p23* | OMIM | *600890* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| Criteria | Consensus | % of max score | |
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 26% | 1:50,000 to 1:200,000. There is an apparent discrepancy between the number of cases diagnosed clinically and the low rate of detection by NBS, raising the possibility of undetected false negative results. |
| Phenotype at birth | Almost never | 83% | The presence of maternal acute fatty liver of pregnancy and hemolysis elevated liver enzymes, low platelet count (HELLP) may be indicative of an LCHAD pregnancy [1,2] Rarely apparent in |
| Burden if untreated | Profound | 88% | Clinical signs include acute and chronic liver failure, cardiomyopathy and skeletal myopathy. There is a high mortality at presentation but developmental delay/MR are not cardinal features [3,4,5,6]. |
| The test | | | |
| Screening test | Yes | 98% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. C16-18 OH acylcarnitine species are elevated [7,8,9]. Visual evaluation of profile is critical to recognize minor abnormalities. |
| Doable in DBS or by physical method | Yes | 96% | See [7]. 2nd tier DNA analysis of DBS is also available [10]. |
| High throughput | Yes | 89% | Up to 500-1,000 specimens per day [7]. |
| Overall cost <$1 | <$1/test | 57% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [11]. |
| Multiple analytes | Yes | 87% | C16-OH, C18:1-OH, C18-OH [8,9]. |
| Secondary targets | Yes | 67% | Trifunctional protein (TFP) deficiency. |
| Multiplex platform | Yes | 75% | For comprehensive review see [7]. |
| The treatment | | | |
| Availability & cost | Limited availability | 78% | Frequent feedings, dietary restriction of long-chin fatty acids, high carbohydrate, MCT oil and carnitine plus dietary supplements require metabolic specialists of limited availability [2,12]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 43% | Few patients treated prospectively with long-term outcome assessment have been reported. 30% continue to have episodes of metabolic decompensation [2,12,13]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 70% | Few patients treated prospectively with long-term outcome assessment have been reported. 30% continue to have episodes of metabolic decompensation [2,12,13]. |
| Benefits of early identification | CLEAR benefits to family and society | 85% | Genetic counseling and prenatal diagnosis are available [14]. Identification of families at-risk for LCHAD offspring allows for monitoring for acute fatty liver of pregnancy [1,3]. |
| Prevention of mortality | Yes | 89% | Despite recurrence of metabolic decompensation with treatment, mortality rate is improved [2,12,13]. |
| Confirmation of diagnosis | Limited availability | 53% | Assay of three activities of TFP enzyme complex (L-3-OH acyl-CoA dehydrogenase, 2-enoyl-CoA- hydratase, and 3-oxoacyl-CoA thiolase) to distinguish from TFP deficiency [2]. 60-70% of cases are homozygous 1528G->C [2,10,14,15]. |
| Acute management | Limited availability | 56% | Well established emergency protocols [2]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 35% | No special food or orphan drug required [2]. |

**Long-chain 3-OH acyl-CoA dehydrogenase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1445 /2100 | % of max score | 69% |
| Rank: | 0.84 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

LCHAD deficiency was among the highest scoring of the panel of conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel and state programs currently not screening for LCHAD deficiency should be strongly encouraged to add this condition to their panel as soon as feasible. Differential diagnosis of secondary targets needs to be considered. Regionalization of analytical services has been adopted already in a few regions.

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| CONDITION | Medium-chain acyl-CoA dehydrogenase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error of metabolism, fatty acid oxidation disorder |
| ETHNICITY | Predominantly Caucasians of northern european ancestry; less frequent in Hispanics; rare in African-Americans; very rare in Orientals. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 31 of 51 states, 53% of annual births (August 2004) |

| Responses: | 90 | Valid scores: | 1,556 | 96% | PubMed references (August 2004): | 801 |
|---|---|---|---|---|---|---|

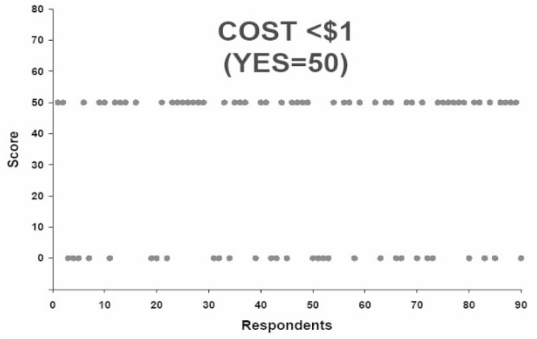
| Gene | *ACDM* | Locus | *1p31* | OMIM | *201450* |
|---|---|---|---|---|---|

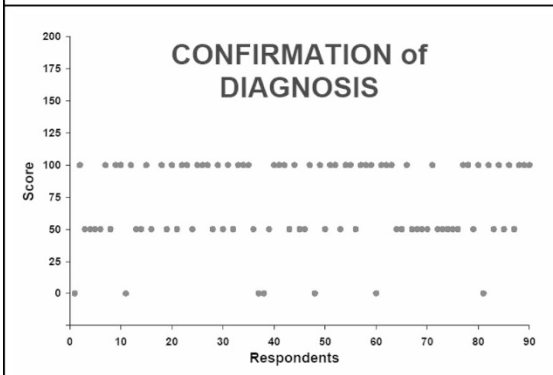
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:25,000 | 78% | MCAD deficiency occurs in 1:10,000-1:15,000 US newborns; higher in Northern European ancestry [1]. |
| Phenotype at birth | Almost never | 91% | Reports of severe neonatal decompensation and sudden unexpected death in exclusively breast-fed newborns [2]. |
| Burden if untreated | Profound | 84% | Mortality is 30-50% at first episode [3]. |
| The test | | | |
| Screening test | Yes (MS/MS) | 100% | First reported in 1990 [4]. |
| Doable in DBS or by physical method | Yes | 99% | See [4]. 2nd tier DNA analysis of DBS is also available [5]. |
| High throughput | Yes | 92% | Up to 500-1,000 specimens per day [6]. |
| Overall cost <$1 | Yes (lack of consensus) (*) | 63% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [7]. |
| Multiple analytes | Yes | 92% | C6, C8, C10:1, C10 acylcarnitines [1,3,4,8,9]. |
| Secondary targets | Yes | 74% | GA2 (multiple defects), M/SCHAD, MCKAT [8]. |
| Multiplex platform | Yes | 78% | For comprehensive review see [6]. |
| The treatment | | | |
| Availability & cost | Widely available | 94% | Avoidance of fasting, aggressive treatment of intercurrent illnesses; carnitine supplementation may be useful [3,9,11]. |
| Efficacy of treatment | Potential to prevent ALL negative consequences | 80% | Most cases diagnosed by NBS remain asymptomatic with avoidance of fasting [12,13]. Still limited long-term data [14]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 90% | Expectation of normal growth and development. Significant prevention of mortality [1,3,8,9,11,14,15]. |
| Benefits of early identification | CLEAR benefit to family & society | 94% | Identification of affected relatives [16], prevention of costs for care of episodes [1,3,9,13] dismissal of abuse allegations [17]. |
| Prevention of mortality | Yes | 99% | Prevention of sudden and unexpected death [2,3,8,11,17]. |
| Confirmation of diagnosis | Limited availability (lack of consensus) (*) | 71% | Plasma acylcarnitines and urine acylglycines [18]; genotyping (~20 labs offer testing for 985A>G; <5 labs provide complete gene sequencing) [18-19]. |
| Acute management | Limited availability | 80% | Well established emergency protocols [3,9,11]. |
| Simplicity of therapy | Periodic involvement of specialist | 77% | No special food or orphan drug required [3,9,11]. |

**Medium-chain acyl-CoA dehydrogenase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | YES | Type | MS/MS |
| 2ary target of higher scoring condition? | | | NO |
| Final score | 1799 /2100 | % of max score | 84% |
| Rank: | 1.00 %ile | | |
| Observed significant discrepancies with literature | | | NO |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency had the highest score of the panel of conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel and state programs currently not screening for MCAD deficiency should be strongly encouraged to add this condition to their panel as soon as feasible. Differential diagnosis of secondary targets needs to be considered. Regionalization of analytical services has been adopted already in a few regions.

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| CONDITION | Medium/short-chain L-3-OH acyl-CoA DH deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | No known ethnic variation. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 6 of 51 states, 8% of annual births (August 2004) |

| Responses: | 21 | Valid scores: | 335 | 89% | PubMed references (August 2004) | 11 |
|---|---|---|---|---|---|---|

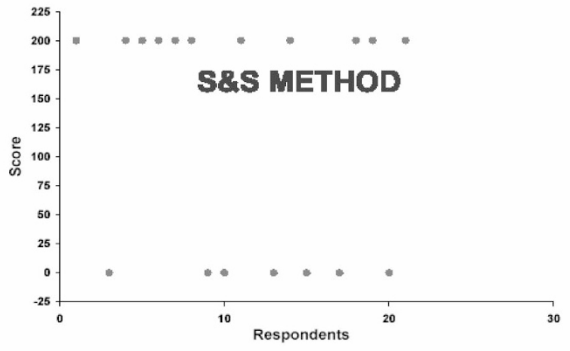
| Gene | *HADHSC* | Locus | *4q22-q26* | OMIM | *607008* |
|---|---|---|---|---|---|

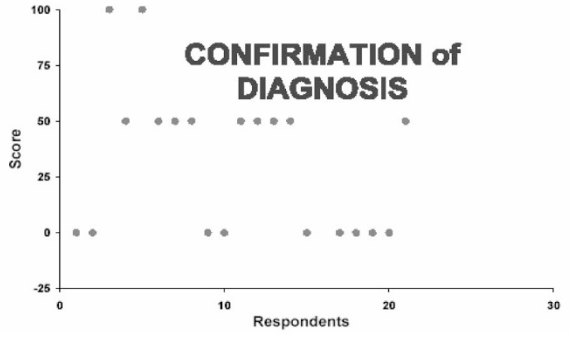
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 9% | Not known; very rare with fewer than 5 cases with two documented mutations in the known M/SCHAD gene [1-3]. |
| Phenotype at birth | Almost never | 97% | Symptoms in patients with SCHAD enzyme deficiency include infection-induced hypoglycemia in combination with mild to absent ketosis [1-6]. |
| Burden if untreated | Severe | 76% | Stress induced hypoglycemia in most cases [1,2]. One case presented as SIDS [3]. |
| The test | | | |
| Screening test | Yes (*) | 61% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary marker is C4-OH [1,5,7,9]. |
| Doable in DBS or by physical method | Yes | 83% | See [7]. |
| High throughput | Yes | 78% | Up to 500-1,000 specimens per day [7]. |
| Overall cost <$1 | <$1/test | 47% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [8]. |
| Multiple analytes | Yes | 67% | C4OH, C8-OH, C8 [5-7]. |
| Secondary targets | Yes | 56% | MCAD, GA-II, MCKAT [5-7]. |
| Multiplex platform | Yes | 67% | See [7] for comprehensive review. |
| The treatment | | | |
| Availability & cost | Limited availability | 67% | Treatment is supportive. Avoidance of fasting is likely to be beneficial, aggressive treatment of intercurrent illnesses. Metabolic specialists should be involved in care [4-6]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 49% | The rarity of M/SCHAD complicates determination of efficacy [1-6]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 50% | Expected to improve outcomes [4-6]. |
| Benefits of early identification | SOME benefits to family and society | 68% | Genetic counseling is available [10]. |
| Prevention of mortality | Yes | 69% | Limited evidence of prevention of mortality. |
| Confirmation of diagnosis | Only a few centers (*) | 33% | DNA mutations have been identified [8]. |
| Acute management | Limited availability | 50% | Well established emergency protocols for FAO disorders are applicable [4]. |
| Simplicity of therapy | Periodic involvement of specialist | 48% | No special foods or orphan drugs are required. Metabolic specialists are of limited availability [4]. |

**Medium/short-chain L-3-OH acyl-CoA DH deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1223 /2100 | % of max score | 58% |
| Rank: | 0.58 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Only a few confirmed cases have been reported. Obviously, the natural history of MSCHAD is not understood, treatment options are similar to other FAO disorders. Specificity and sensitivity of acylcarnitine profiling are undetermined, not a single case has been detected prospectively. For these reasons, M/SCHAD is not recommended for inclusion in the uniform panel. However, a profile suggestive of a possible diagnosis of M/SCHAD is clinically significant and should be reported when detected.

**REFERENCES AND WEB SITES**


| | |
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| 10 | Matern D et al. Medium-chain acyl-coenzyme A dehydrogenase deficiency (as of 01-27-2003). Gene Reviews, http://www.geneclinics.org. |

| CONDITION | Medium-chain ketoacyl-CoA thiolase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | One Japanese patient has been described [1]. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 2 of 51 states, 1% of annual births (August 2004) |

| Responses: | 23 | Valid scores: | 853 | | PubMed references (August 2004) | 23 |
|---|---|---|---|---|---|---|

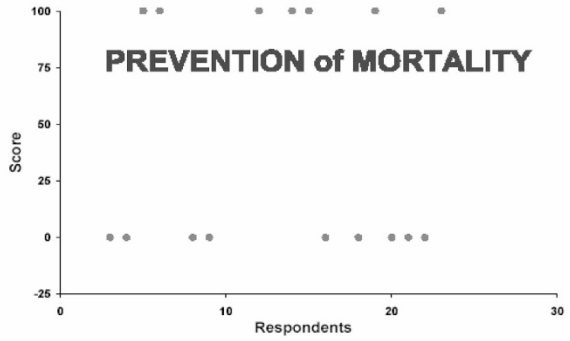
| Gene | *MCKAT* | Locus | *unknown* | OMIM | *602199* |
|---|---|---|---|---|---|

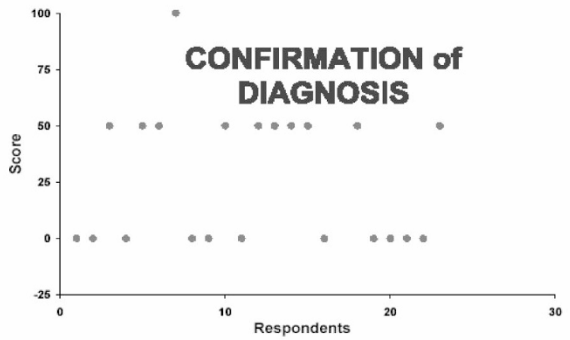
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 9% | One case has been described [1]. |
| Phenotype at birth | <25% of cases | 93% | Patient presented at day 2 with vomiting, dehydration, metabolic acidosis, liver dysfunction and terminal rhabdomyolysis with myoglobinuria [1]. |
| Burden if untreated | Severe | 83% | The one patient died on day 13 of life [1]. |
| The test | | | |
| Screening test | Yes | 65% | MS/MS; precursor ion scan of m/z 85 for acylcarnitine profiling. Primary marker is C8 [1,2]. |
| Doable in DBS or by physical method | Yes | 84% | Yes [2]. |
| High throughput | Yes | 84% | Up to 500-1,000 specimens per day [3]. |
| Overall cost <$1 | No (>$1/test) | 53% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [4]. |
| Multiple analytes | Yes | 74% | C10, C12 acylcarnitines [1]. |
| Secondary targets | Yes | 67% | M/SCHAD. |
| Multiplex platform | Yes | 74% | Yes, see [2] for comprehensive review. |
| The treatment | | | |
| Availability & cost | Limited availability | 63% | Avoidance of fasting; aggressive treatment of intercurrent illnesses and other generic measures applicable to FAO disorders [3]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 43% | Unknown. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 42% | Unknown. |
| Benefits of early identification | SOME benefits to family and society | 62% | Unknown. |
| Prevention of mortality | No (lack of consensus) (*) | 44% | Unknown. |
| Confirmation of diagnosis | Only a few centers (lack of consensus) (*) | 27% | Plasma acylcarnitines, urine organic acids and acylglycines [1]. Enzymology is only option in vitro until the gene is identified. |
| Acute management | Limited availability | 41% | Avoidance of fasting; aggressive treatment of intercurrent illnesses. |
| Simplicity of therapy | Regular involvement of specialist | 39% | Metabolic physicians would be needed and are of limited availability. |

**Medium-chain ketoacyl-CoA thiolase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1170 /2100 | % of max score | 56% |
| Rank: | 0.52 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Only one confirmed case has been reported. Obviously, the natural history of MCKAT is not understood, treatment options are similar to other FAO disorders. Specificity and sensitivity of acylcarnitine profiling are undetermined, not a single case has been detected prospectively. For these reasons, MCKAT is not recommended for inclusion in the uniform panel. However, a profile suggestive of a possible diagnosis of MCKAT is clinically significant and should be reported when detected.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| 3 | National Newborn Screening & Genetics Resource Center: Current newborn conditions by state (as of 07-05-04), http://genes-r-us.uthscsa.edu/. |
| 4 | GeneTests Laboratory Directory, http://www.geneclinics.org/; or UCSD Biochemical Genetics Test List, http://biochemgen.ucsd.edu/ucsdw3bg/. |

| CONDITION | Short-chain acyl-CoA dehydrogenase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 18 of 51 states, 29% of annual births (August 2004) |

| Responses: | 51 | Valid scores: | 289 | 31% |
|---|---|---|---|---|

| PubMed references (August 2004) | 129 |
|---|---|

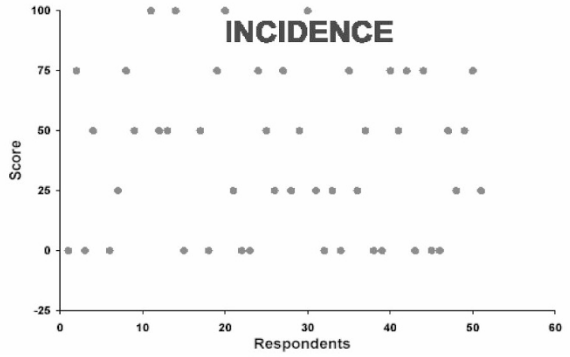
| Gene | *ACLDS* | Locus | *12q22-ter* | OMIM | *201470* |
|---|---|---|---|---|---|

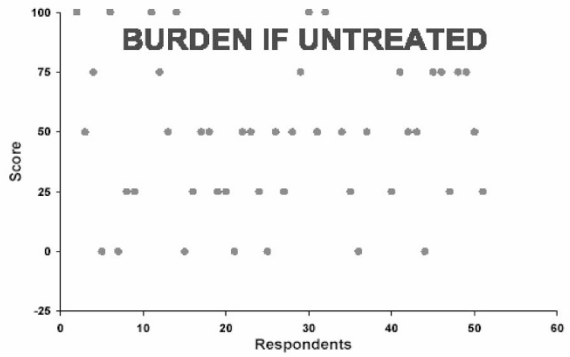
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 40% | 1:40,000 - 100,000 [1,2,3,4]. |
| Phenotype at birth | Almost never | 88% | Most cases present in the first 3 months of life [1]. |
| Burden if untreated | Moderate (lack of consensus) (*) | 47% | The phenotype is variable. 50% of cases present with hypotonia and developmental delay. Others may have seizures, acidosis, vomiting, and failure to thrive. One of 20 cases was a demise. Asymptomatic cases have been identified [1,5]. |
| The test | | | |
| Screening test | Yes | 92% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary marker is C4 [9,10]. |
| Doable in DBS or by physical method | Yes | 98% | See [10]. |
| High throughput | Yes | 90% | Up to 500-1,000 specimens per day [10]. |
| Overall cost <$1 | <$1/test | 59% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [11]. |
| Multiple analytes | Yes | 87% | Other species are required for differential diagnosis. |
| Secondary targets | Yes | 63% | IBG, GA2, ethylmalonic encephalopathy [9,10]. |
| Multiplex platform | Yes | 76% | See [10] for a comprehensive review. |
| The treatment | | | |
| Availability & cost | Limited availability | 76% | Treatment is supportive [1]; avoidance of fasting is likely to be beneficial; low fat diets and riboflavin have not helped; metabolic specialists should be involved in care. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 32% | The highly variable phenotype including asyptomatic individuals and the rarity of SCAD complicates determination of efficacy [8]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 39% | Anecdotal reports of response to supportive treatment see lack of consensus on criterion "burden if untreated above." |
| Benefits of early identification | SOME benefits to family and society | 48% | Genetic counseling and prenatal diagnosis are available but rarely requested. |
| Prevention of mortality | No | 47% | Limited evidence of prevention of mortality. |
| Confirmation of diagnosis | Only a few centers | 40% | Measurement of acyl-CoA dehydrogenase activities with MCAD activity blocked is of very limited availability. Fibroblast acylcarnitine profiling and DNA sequencing are available. Elevations of ethylmalonic acid and methyl succininc acid are seen in the classic form [12,13]. |
| Acute management | Limited availability | 55% | Sodium bicarbonate for acidosis and dextrose/glucose for hypogycemia are part of the emergency protocols available for SCAD [1]. |
| Simplicity of therapy | Periodic involvement of specialist | 43% | Metabolic specialists are required for management. |

**Short-chain acyl-CoA dehydrogenase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | NO |
| Final score | 1252 /2100 | % of max score | 60% |
| Rank: | 0.63 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Evidence is accumulating that classic SCAD is distinguished from variant SCAD with the mild or asymptomatic phenotype by both screening cut-offs and DNA mutations and variants. Gene polymorphisms of unknown clinical significance are common [14].

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| CONDITION | Trifunctional protein deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 11 of 51 states, 25% of annual births (August 2004) |

| Responses: | 42 | Valid scores: | 719 | 95% | PubMed references (August 2004) | 26 |
|---|---|---|---|---|---|---|

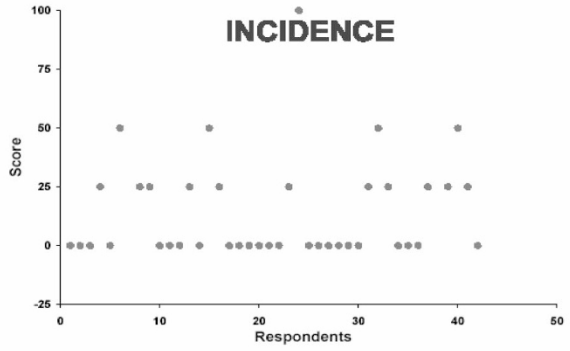
| Gene | *HADHB* | Locus | *2p23* | OMIM | *600890 143450* |
|---|---|---|---|---|---|

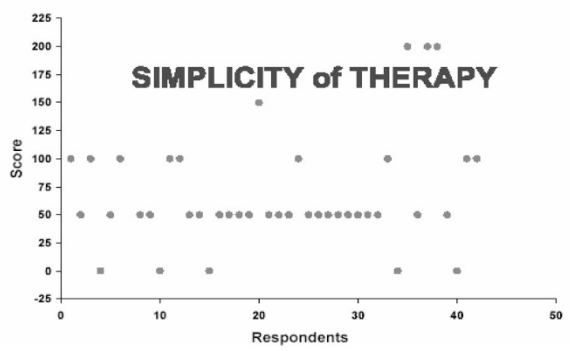
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 14% | Unknown. Fewer than 20 cases have been described [1-5]. |
| Phenotype at birth | Almost never | 83% | Rarely apparent in the neonatal period but early onset has been reported [6]. |
| Burden if untreated | Profound | 93% | Hypoketotic hypoglycemia leading to cardiomyopathy and neuromuscular disease. A Reye-like syndrome and sudden death can ensue. Milder phenotypes are now being appreciated [1-10]. |
| The test | | | |
| Screening test | Yes | 96% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. C16-18 OH acylcarnitine species are elevated [7,8,9]. Visual evaluation of profile is critical to recognize minor abnormalities [7,11,12,13]. |
| Doable in DBS or by physical method | Yes | 95% | See [7,9]. 2nd tier DNA analysis of DBS is also available and can distinguish between LCHAD and TFP [7,12]. |
| High throughput | Yes | 88% | Up to 500-1,000 specimens per day [12]. |
| Overall cost <$1 | <$1/test | 51% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [14]. |
| Multiple analytes | Yes | 85% | C16-OH, C18:1-OH, C18-OH, C16, C14, C14:1 [11,12]. |
| Secondary targets | Yes | 65% | LCHAD, VLCAD. |
| Multiplex platform | Yes | 72% | See [12] for comprehensive review. |
| The treatment | | | |
| Availability & cost | Limited availability | 81% | Frequent feedings; dietary restricition of long-chain fatty acids; high carbohydrate; MCT oil and carnitine plus dieatary supplements require metabolic specialists of limited availability [15,16]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 42% | Few patients have been reported who are treated prospectively with long-term outcome asessment [15]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 75% | Few patients who are treated prospectively with long-term outcome assessment have been reported [15]. |
| Benefits of early identification | Clear benefits to family and society | 85% | Genetic counseling and prenatal diagnosis are available. |
| Prevention of mortality | Yes | 85% | Appropriate management of intercurrent illness and ongoing treatment minimize lethality [12, 13]. |
| Confirmation of diagnosis | Limited availability | 45% | Demonstration of significantly decreased activity of two of the three enzymes of the TFP complex. DNA testing is available [7]. |
| Acute management | Limited availability | 54% | Well established emergency protocols [15, 16]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 34% | No special food or orphan drug required [15,16]. |

**Trifunctional protein deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1418 /2100 | % of max score | 68% |
| Rank: | 0.81 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

TFP deficiency scored high among conditions included in the survey. This condition meets the criteria for inclusion in the uniform panel. State programs currently not screening for TFP deficiency should be strongly encouraged to add this condition to their panel as soon as feasible.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| 13 | Van Hove JL et al. Acylcarnitines in plasma and blood spots of patients with long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. J Inherit Metab Dis 2000;23:571-82. |
| 14 | National Newborn Screening and Genetics Resource Center. Current newborn screening conditions by state (as of 7-05-04). http://genes-r-us.uthscsa.edu/. |
| 15 | Roe CR et al. Mitochondrial fatty acid oxidation disorders. In: Scriver CR et al. eds. The Metabolic and Molecular Basis of Inherited Disease, 8th ed. New York; McGraw-Hill, 2001:2297-326. |
| 16 | Gillingham MB et al. Optimal dietary therapy of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. Mol Genet Metab. 2003;79:114-23. |

| CONDITION | Very long-chain acyl-CoA dehydrogenase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of fatty acid metabolism |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

| Responses: | 58 | Valid scores: | 1,019 | 98% |
|---|---|---|---|---|

| PubMed references (August 2004) | 269 |
|---|---|

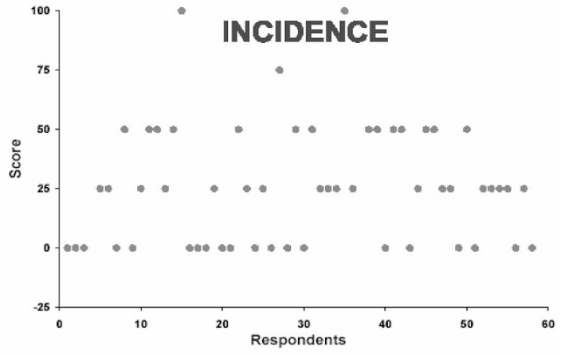
| Gene | *ACADVL* | Locus | *17p11.2-p11.1* | OMIM | *201475* |
|---|---|---|---|---|---|

**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 26% | Unknown [1]. Detection rate by NBS higher than expected from clinical ascertainment [8]. |
| Phenotype at birth | Almost never | 85% | The infantile (50% of cases) form presents with nonketotic hypoglycemia, hypertrophic cardiomyopathy, and skeletal myopathy. Infants have rarely presented in the first 24 hrs. A later presenting infantile form (30% of cases) lacks cardiac involvement. 20% (though proportion is increasing as more cases are found) present as adolescents or adults with muscle fatigue, myoglobinuria and rhabdomyolysis [1-9]. |
| Burden if untreated | Profound | 87% | Untreated infants with the infantile form die in first year. The late infantile hepatic form is also lethal if not treated [1]. Asymptomatic adults have been described [8]. |
| The test | | | |
| Screening test | Yes | 98% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary marker is C14:1 [10,11]. |
| Doable in DBS or by physical method | Yes | 96% | See [6,7]. Allelic heterogeneity precludes molecular testing. |
| High throughput | Yes | 89% | Up to 500-1,000 specimens per day [11]. |
| Overall cost <$1 | <$1/test | 56% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [12]. |
| Multiple analytes | Yes | 88% | C14:1, C14, C16, C16:1 and C18:1 [11]. |
| Secondary targets | Yes | 68% | LCHAD, TFP [11]. |
| Multiplex platform | Yes | 73% | For comprehensive review see [11]. |
| The treatment | | | |
| Availability & cost | Limited availability | 82% | Avoidance of fasting, aggressive treatment of intercurrent illnesses, carnitine supplementation, diet high in carbohydrates and medium chain triglycerides [1,13,15,17]. |
| Efficacy of treatment | Potential to prevent Most negative consequences | 50% | Clear evidence of reduced lethality and successful treatment of cardiomyopathy [13,17]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 75% | Identification of affected relatives [8], prevention of costs for care of episodes [1,13,17] dismissal of abuse allegations. |
| Benefits of early identification | Clear benefits to family and society | 85% | Genetic counseling and prenatal diagnosis are available. |
| Prevention of mortality | Yes | 94% | Long-term survival following presymptomatic treatment has been documented [13,14]. |
| Confirmation of diagnosis | Limited availability | 54% | DNA testing may discriminate a milder later-onset form that preserves some enzyme activity from the more severe infantile form [14,16]. |
| Acute management | Limited availability | 57% | Well established emergency protocols [3,9,11]. |
| Simplicity of therapy | Periodic involvement of specialist (lack of consensus) (*) | 42% | No special food or orphan drug required [3,9,11]. |

**Very long-chain acyl-CoA dehydrogenase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page





**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1493 /2100 | % of max score | 71% |
| Rank: | 0.89 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

VLCAD deficiency was among the highest scoring of the panel of conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel and state programs currently not screening for VLCAD deficiency should be strongly encouraged to add this condition to their panel as soon as feasible. Regionalization of analytical services has been adopted already in a few regions.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| 17 | Cox GF et al. Reversal of severe hypertrophic cardiomyopathy and excellent neuropsychologic outcome in very-long-chain acyl-coenzyme-A dehydrogenase deficiency. J Pediatr 1998;133:247. |

# ORGANIC ACIDURIAS

| CONDITION | 2-Methylbutyryl-CoA dehydrogenase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | High incidence in Hmong population. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 17 of 51 states, 28% of annual births (August 2004) |

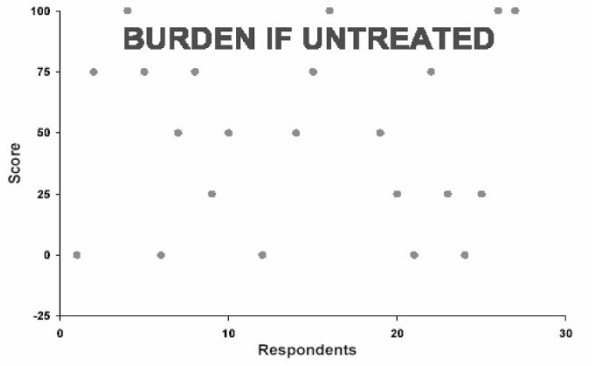
| Responses: | 27 | Valid scores: | 400 | 82% | PubMed references (August 2004) | 8 |
|---|---|---|---|---|---|---|

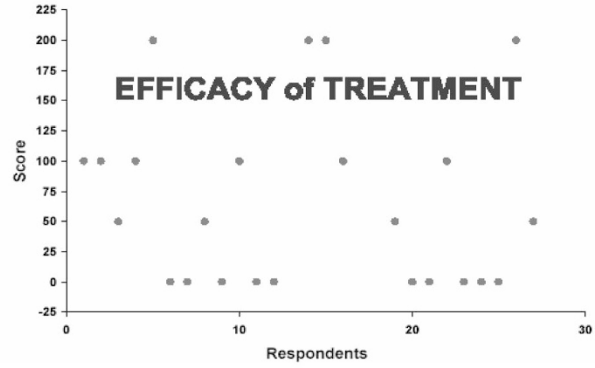
| Gene | *ACADSB* | Locus | *10q25-q26* | OMIM | *600301* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 13% | Rare in general US population (case reports only); high incidence in Hmong population [1, 2, 3]. |
| Phenotype at birth | Almost never | 95% | Severe neonatal decompensation reported. Some cases are asymptomatic [1,2,3]. |
| Burden if untreated | Moderate (lack of consensus) (*) | 53% | Natural history poorly understood. [1,2,3]. |
| The test | | | |
| Screening test | Yes | 82% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling; differential diagnosis of elevated C5 is required [3,4,5]. |
| Doable in DBS or by physical method | Yes | 93% | Yes [3,5]. |
| High throughput | Yes | 85% | Up to 500-1000 tests per day [5]. |
| Overall cost <$1 | <$1/test | 52% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [6]. |
| Multiple analytes | Yes | 68% | Isolated elevation of C5 acylcarnitine (representing primarily 2-methylbutyrylcarnitine in this disorder) [3]. |
| Secondary targets | Yes | 58% | Primary target is IVA [3,8]. |
| Multiplex platform | Yes | 73% | Yes [4,5]. |
| The treatment | | | |
| Availability & cost | Limited availability | 58% | Protein restricted diet; carnitine supplementation; avoidance of fasting less clear [1,2,3]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (lack of consensus) (*) | 33% | Outcome is dependent on early identification and treatment [1,2,3]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 36% | Outcome is dependent on early identification and treatment [1,2,3]. |
| Benefits of early identification | SOME benefits to family and society | 50% | Genetic counseling and identification of at-risk family members is available, dismissal of abuse cases [3,8]. |
| Prevention of mortality | No | 31% | Unknown but expected to improve mortality [9]. |
| Confirmation of diagnosis | Limited availability | 42% | Urine acylglycines, urine organic acids, plasma acylcarnitines; cell-based in vitro studies in fibroblast cultures; specific enzyme assay and molecular genetic analysis available on a research basis only [3,7,8]. |
| Acute management | Limited availability | 42% | Well established emergency protocols [9]. |
| Simplicity of therapy | Regular involvement of specialist | 32% | Dietary management requires involvement of metabolic specialists who are of limited availability [9]. |

**2-Methylbutyryl-CoA dehydrogenase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1124 /2100 | % of max score | 54% |
| Rank: | 0.39 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Newly discovered condition, very limited knowledge of natural history. This is a clinically significant condition detected by acylcarnitine profiling to be included in the differential diagnosis of primary targets.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| 6 | National Newborn Screening and Genetics Resource Center. Current newborn conditions by state (as of 07-05-04), http://genes-r-us.uthscsa.edu/. |
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| CONDITION | 2-Methyl 3-hydroxy butyric aciduria |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | Only a few cases described worldwide. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 9 of 51 states, 8% of annual births (August 2004) |

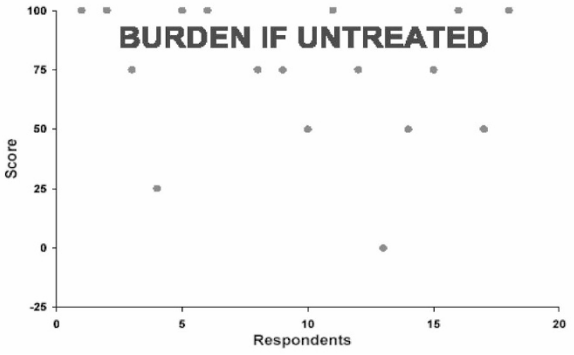
| Responses: | 18 | Valid scores: | 313 | 97% | PubMed references (December 2004) | 7 |
|---|---|---|---|---|---|---|

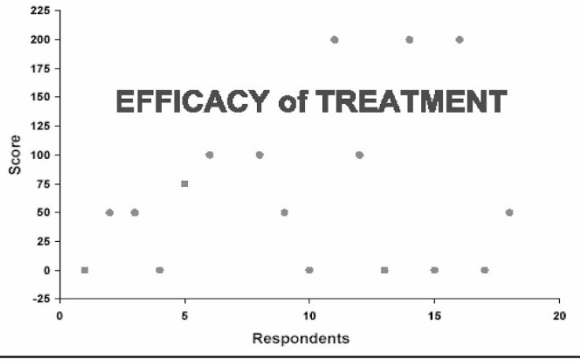
| Gene | *HADH2* | Locus | *11q22.3-q23.1* | OMIM | *300256; 300438* |
|---|---|---|---|---|---|

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 6% | The first case was described in 2000 [1]. Seven cases have been described [1-3,5,6,10]. |
| Phenotype at birth | Almost never | 94% | Rarely. One patient presented with metabolic acidosis on day 2 of life [1]. |
| Burden if untreated | Severe (*) | 74% | Psychomotor retardation in all. Loss of mental and motor skills in 5 (all males). One report of a female and a male with developmental delay but without regression. Epilepsy and blindness in 4 cases [1-5,10]. |
| The test | | | |
| Screening test | Yes | 65% | MS/MS is presumed to identify patients but none have been identified prospectively (retrospective analysis of the reported patient's original NBS cards was not attempted/reported) [6]. |
| Doable in DBS or by physical method | Yes | 88% | Yes [6]. |
| High throughput | Yes | 71% | Up to 500-1000 tests per day [6]. |
| Overall cost <$1 | No (>$1/test) | 41% | Cost likely higher if MS/MS is used to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [11]. |
| Multiple analytes | Yes | 59% | C5:1-carnitine (representing tiglylcarnitine) and C5-OH-carnitine may be mildly elevated (representing primarily 2-methyl 3-hydroxybutyrylcarnitine) [1-3,5,6,12]. |
| Secondary targets | Yes | 59% | Primary target for C5-OH acylcarnitine: 3MCC. Other secondary targets: HMG-CoA lyase deficiency, biotinidase deficiency, beta-ketothiolase deficiency, 3-methylglutaconic acid hydratase deficiency, 3-methylglutaconic aciduria type I, biotinidase deficiency, and ß-ketothiolase deficiency [6]. |
| Multiplex platform | Yes | 59% | Yes [6]. |
| The treatment | | | |
| Availability & cost | Limited availability | 64% | Low protein, high carbohydrate diet with isoleucine restriction [1,10]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (*) | 35% | Presumed to be effective, no case has been detected prospectively so far. In 5 of 7 cases, treatment has been reported, and clinical status has been stabilized [1,2,5,10]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 50% | Presumed to be effective; no case has been detected prospectively so far. The first patient reported [1] has died since being reported; other patients have shown variable to no improvement [2,9]. |
| Benefits of early identification | SOME benefits to family and society | 69% | Genetic counseling is available and prenatal diagnosis is feasible but not yet done [8,9]. |
| Prevention of mortality | Yes | 53% | Not known. No patients have been identified prospectively. 5 of 7 cases have been treated [2,4,10]. |
| Confirmation of diagnosis | Limited availability | 44% | Urine acylglycines, urine organic acids, and plasma acylcarnitines allow decision whether NBS is false positive. Confirmation by specific enzyme assay and HADH2 gene sequencing is of limited availability on a research basis only [2,9]. |
| Acute management | Limited availability | 50% | Symptomatic. Emergency protocols as established for other organic acidemias [2,4,8,10]. |
| Simplicity of therapy | Regular involvement of specialist | 29% | Metabolic physicians are required for dietary management and care coordination in collaboration with PCP [1,2,8]. |

**2-Methyl 3-hydroxy butyric aciduria**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1132 /2100 | % of max score | 54% |
| Rank: | 0.41 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Newly discovered condition, very limited knowledge of natural history. This is a clinically significant condition detected by acylcarnitine profiling to be included in the differential diagnosis of primary targets.

**REFERENCES AND WEB SITES**


| | |
|---|---|
| 1 | Zschocke J et al. Progressive infantile neurodegeneration caused by 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency: a novel inborn error of branched-chain fatty acid and isoleucine metabolism. Pediatr Res 2000;48:852-5. |
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| 11 | National Newborn Screening and Genetics Resource Center. Current newborn conditions by state (as of 07-05-04), http://genes-r-us.uthscsa.edu/. |
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| CONDITION | 3-hydroxy 3-methyl glutaric aciduria (HMG) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | Panethnic; higher in Saudi Arabia. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 21 of 51 states, 33% of annual births (August 2004) |

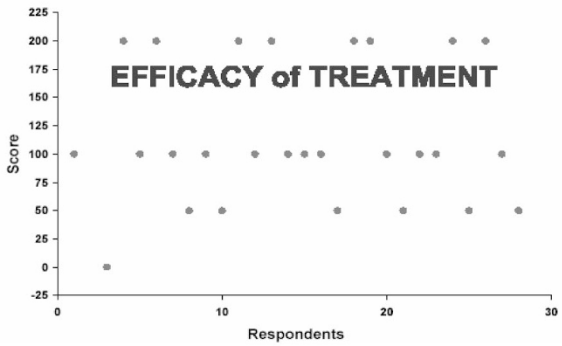
| Responses: | 28 | Valid scores: | 482 | 96% | PubMed references (August 2004) | 8 |
|---|---|---|---|---|---|---|

| Gene | *HMGCL* | Locus | *1pter-p33* | OMIM | *246450* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | <1:100,000 | 11% | Rare; no population data available. Higher in Saudi Arabia [1,2]. |
| Phenotype at birth | Almost never | 91% | 20 - 50% presented in the first week; most of the rest by age 2 yrs [1-4]. |
| Burden if untreated | Severe | 84% | Severe hypoketotic hypoglycemia and acidosis, hyperammonemia and epilepsy leading to death in 20% [2-4]. |
| The test | | | |
| Screening test | Yes | 89% | MS/MS. Reported in 1990 [5,6]. |
| Doable in DBS or by physical method | Yes | 93% | Allelic heterogeneity limits molecular second tier tests [7]. |
| High throughput | Yes | 74% | Up to 500-1,000 tests per day [6]. |
| Overall cost <$1 | No (>$1/test) | 50% | Cost likely higher if MS/MS is used to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) h [8]. |
| Multiple analytes | Yes | 64% | C5-OH, C6-OH/DC, C6-DC methyl-glutaryl carnitine [6,9]. |
| Secondary targets | Yes | 60% | 2M3HBA, 3MGL [6]. |
| Multiplex platform | Yes | 65% | For comprehensive review see [6]. |
| The treatment | | | |
| Availability & cost | Limited availability | 76% | Acute management of lactic acidosis with IV glucose and bicarbonate. Leucine restriction; avoidance of protein rich and ketogenic diets [2,10,11]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences (lack of consensus) (*) | 57% | Early diagnosis and treatment prevents abnormal development [2,10,11]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 69% | Significant prevention of mortality [2,10,11]. |
| Benefits of early identification | CLEAR benefits to family and society | 79% | Genetic counseling, identification of relatives, prevention of costs for care of episodes, prenatal diagnosis, dismissal of abuse allegations [10]. |
| Prevention of mortality | Yes | 89% | Significant prevention of mortality [2,10,11]. |
| Confirmation of diagnosis | Limited availability | 56% | Plasma AC (~20 labs in the US) urine OA (>50 labs in the US) [12]. |
| Acute management | Limited availability | 59% | Well established emergency protocols [2,10,11,13]. |
| Simplicity of therapy | Periodic involvement of specialist (lack of consensus) (*) | 50% | No special food or orphan drugs [2,10,11,13]. |

**3-hydroxy 3-methyl glutaric aciduria (HMG)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page





**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1420 /2100 | % of max score | 68% |
| Rank: | 0.82 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Few cases are described in the US. Based on the generic treatment of other conditions treated for lactic acidosis and leucine restriction, this condition was placed in the core condition panel.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| 2 | Mitchell GA et al. Inborn Errors of Ketone Body Metabolism. In: Scriver CR et al. (eds) The Metabolic and Molecular Bases of Inherited Disease, 8th ed. McGraw-Hill, New York, 2001;2327-56. |
| 3 | Wysocki SJ, Hahnel R. 3-Hydroxy-3-methylglutaryl-coenzyme a lyase deficiency: a review. J Inherit Metab Dis 1986;9:225-33. |
| 4 | Gibson KM, Breuer J, Nyhan WL. 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: review of 18 reported patients. Eur J Pediatr 1988;148:180-6. |
| 5 | Millington DS et al. Tandem mass spectrometry: A new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism. J Inherit Metabol Dis 1990;13:321. |
| 6 | Chace DH et al. Use of mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem 2003;49:1797-817. |
| 7 | Mitchell GA et al. HMG CoA lyase deficiency: identification of five causal point mutations in codons 41 and 42, including a frequent Saudi Arabian mutation, R41Q. Am J Hum Genet 1998;62:295-300. |
| 8 | National Newborn Screening and Genetics Resource Center. Current newborn conditions by state (as of 07-05-04), http://genes-r-us.uthscsa.edu/. |
| 9 | Hammond J et al. 3-hydroxy-3-methylglutaric, 3-methylglutaconic and 3-methylglutaric acids can be non-specific indicators of metabolic disease. J Inherit Metab Dis 1984;7(suppl 2):117-8. |
| 10 | Seashore MR. The Organic Acidemias: An Overview Gene Reviews (as of 12-9-03), www.geneclinics.org |
| 11 | Dixon MA et al. Intercurrent illness in inborn errors of metabolism. Arch Dis Child 1992;67:1387. |
| 12 | Gene Tests Laboratory Directory, http://www.geneclinics.org/; or UCSD Biochemical Genetics Test List, http://biochemgen.ucsd.edu/. |
| 13 | Stacey TE et al. Dizygotic twins with 3-hydroxy-3-methylglutaric adicuria: unusual presentation, family studies and dietary management Eur J Pediatr 1985;144:177. |

| CONDITION | 3-Methylglutaconic aciduria (type I - hydratase deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | No known ethnic variation. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 13 of 51 states, 19% of annual births (August 2004) |

| Responses: | 21 | Valid scores: | 359 | 95% | PubMed references (August 2004) | 95 |
|---|---|---|---|---|---|---|

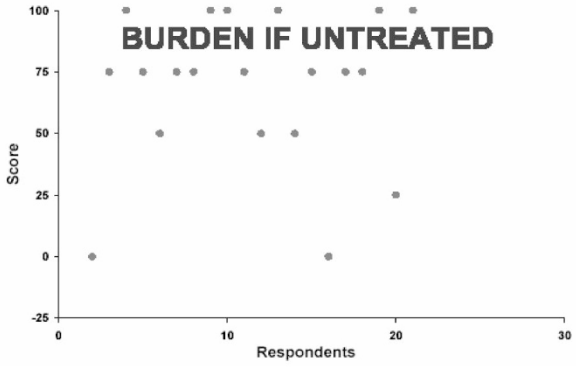
| Gene | *AUH* | Locus | *9?* | OMIM | *250950* |
|---|---|---|---|---|---|

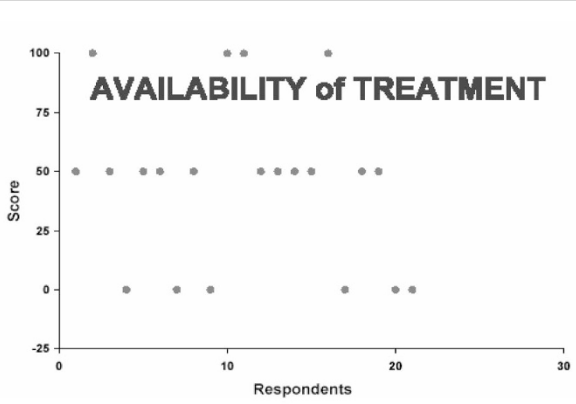
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 10% | Incidence not known but less 1:100,000; rare [1]. |
| Phenotype at birth | Almost never | 90% | Rarely; cardiac abnormalities may be apparent at birth, though not for type 1 (hydratase deficiency) [2,3]. |
| Burden if untreated | Severe (lack of consensus) (*) | 69% | Highly variable with severe neurological dysfunction or cardiac failure in more common types, though some remain asymptomatic throughout life [4-9]. |
| The test | | | |
| Screening test | Yes | 68% | MS/MS first reported in 1990 for type 1, the only 3MGA with associated CoA ester elevations [10]. |
| Doable in DBS or by physical method | Yes | 86% | Yes [11]. |
| High throughput | Yes | 71% | Up to 500-1000 tests per day [11]. |
| Overall cost <$1 | No (>$1/test) | 48% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [12]. |
| Multiple analytes | Yes | 59% | 3-hydroxyisovalerylcarnitine (C5OH), C5-OH methylcrotonyl carnitine [11]. |
| Secondary targets | Yes | 59% | Multiple subtypes of MGA, 3MCC, HMG [10,11]. |
| Multiplex platform | Yes | 58% | Yes [11]. |
| The treatment | | | |
| Availability & cost | Limited availability (lack of consensus) (*) | 45% | Dietary management is variable with MGA subtypes. Low protein diets and avoidance of fasting are central to hydratase deficiency management. Metabolic physicians to resolve subtypes are of limited availability [1-3]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 33% | Efficacy varies with subtypes. Supportive care for all types. Carnitine supplementation and restricted leucine benefits some with Type 1 [1-3,5]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 40% | Treatment can prevent motor delay and brain injury during catabolic crises [1-3,5]. |
| Benefits of early identification | SOME benefits to family and society | 64% | Genetic counseling available and prenatal diagnosis for some subtypes is available [11,12]. |
| Prevention of mortality | No | 21% | Mortality may be reduced in type II with careful management of diet and cardiomyopathy but lethality is not a documented problem. |
| Confirmation of diagnosis | Limited availability | 45% | Plasma acylcarnitines (~20 labs in the US) [13-15]. |
| Acute management | Limited availability | 48% | Metabolic physicians for several subtypes with management protocols for subphenotypes [1,2]. |
| Simplicity of therapy | Regular involvement of specialist | 32% | Metabolic physicians for care coordination and specialists for other features of disease [1,2]. |

### 3-Methylglutaconic aciduria

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1057 /2100 | % of max score | 50% |
| Rank: | 0.34 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Differential diagnosis of 3-methylglutaconic aciduria includes: Type I (3MG-CoA hydratase deficiency), the primary target of 3MGA screening, that is characterized by macrocephaly and delayed speech development. Type II (Barth syndrome, X-linked) presents with cardiomyopathy, neutropenia and growth retardation. Type III is a rare condition affecting patients of Iraqi-Jewish origin with progressive neurologic deterioration. Type IV is a highly variable phenotype with cardiomyopathy, hepatic dysfunction, and neurological manifestations presenting at virtually any age. Lactic acidosis, hypoglycemia, and hyperammonemia are common findings. A number of cases have been related to mitochondrial respiratory chain disorders. Elevated methylglutaconic acid has been observed in Smith-Lemli-Opitz syndrome.

**REFERENCES AND WEB SITES**


| | |
|---|---|
| 1 | Sweetman L et al. Branched chain organic acidurias. In: Scriver CR et al (eds) The Metabolic and Molecular Basis of Inherited Disease, 8th ed. McGraw-Hill, New York, 2001;2125-2163. |
| 2 | Rousson R, Guibaud P. Long term outcome of organic acidurias: A survey of 105 French cases (1967-1983). J Inherit Metab Dis 1984;7(suppl 1):10-12. |
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| 4 | Costeff H, Elpeleg ON. 3-Methylglutaconic aciduria, type 3. Brain Dev 1995;17:226. |
| 5 | Gibson KM et al. Variable clinical presentation in three patients with 3-methylglutaconyl-coenzyme A hydratase deficiency. J Inherit Metab Dis 1998;21(6):631-638. |
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| 9 | Gibson KM et al. Multiple syndromes of 3-methylglutaconic aciduria. Pediatric Neurology. 1993;9(2):120-3. |
| 10 | Millington DS et al. Tandem mass spectrometry: A new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism. Jour Inherited Metabolic Disease 1990;13:321. |
| 11 | Chace DH et al. Use of mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem 2003;49:1797-817. |
| 12 | National Newborn Screening and Genetics Resource Center. Current newborn conditions by state (as of 07-05-04), http://genes-r-us.uthscsa.edu/. |
| 13 | Chitayat D et al. 3-Methylglutaconic aciduria: a marker for as yet unspecified disorders and the relevance of prenatal diagnosis in a 'new' type ('type 4'). J Inherit Metab Dis. 1992;15(2):204-12. |
| 14 | Sweetman L. Prenatal diagnosis of the organic acidurias. J Inher Metab Dis 1984;7(suppl 1):18-22. |
| 15 | Gene Tests Laboratory Directory, http://www.geneclinics.org/; or UCSD Biochemical Genetics Test List, http://biochemgen.ucsd.edu/ |

| CONDITION | 3-Methylcrotonylglycinuria (3-methylcrotonyl-CoA carboxylase deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | No known ethnic variability. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 21 of 51 states, 33% of annual births (August 2004) |

| Responses: | 48 | Valid scores: | 830 | 96% | PubMed references (August 2004) | 148 |
|---|---|---|---|---|---|---|

| Gene | *MCCC1 MCCC2* | Locus | *3q25-q27 5q12-q13* | OMIM | *210200; 609010; 210210; 609014* |
|---|---|---|---|---|---|

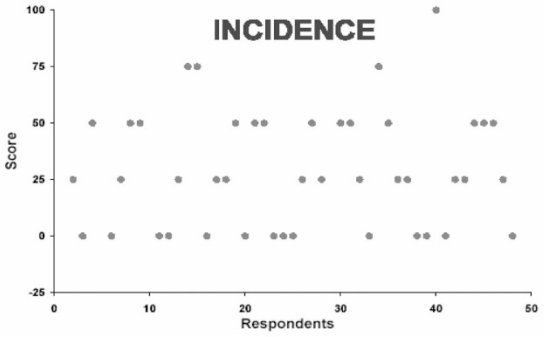
**SURVEY SCORES**

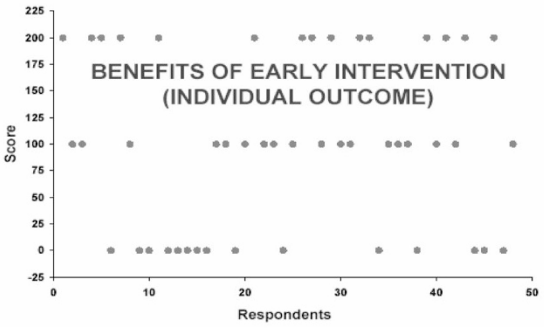
| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 30% | Considered rare, number of cases diagnosed by NBS is higher (1:50,000 - 75,000) than expected [1,2]. |
| Phenotype at birth | Almost never | 92% | Rarely, if ever, present at birth, usually between 1 and 3 years of age [1-5]. |
| Burden if untreated | Moderate | 53% | Severe ketoacidosis, hypoglycemia hyperammonemia can lead to severe neurological damage, coma and death. Isolated hypotonia due to carnitine deficiency may also occur [1,2]. |
| The test | | | |
| Screening test | Yes | 94% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Hydroxy isovalerylcarnitine is highly specific [2,6]. |
| Doable in DBS or by physical method | Yes | 98% | Yes [7]. |
| High throughput | Yes | 87% | Up to 500-1000 tests per day [7]. |
| Overall cost <$1 | <$1/test | 55% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [8]. |
| Multiple analytes | Yes | 73% | 3-hydroxyisovalerylcarnitine (C5OH) [9]. |
| Secondary targets | Yes | 64% | Other disorders of leucine metabolism, MCD [1,6,7]. |
| Multiplex platform | Yes | 73% | Yes [7]. |
| The treatment | | | |
| Availability & cost | Limited availability | 77% | Modest restriction of leucine intake is often done but there is lack of consensus as to whether it is warranted. Carnitine supplementation to prevent deficiency [1,10-13]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 57% | There is lack of consensus for use of leucine restricted diets. Correct treatment of acute episodes prevents disability in almost all cases [1,10-13]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome (lack of consensus) (*) | 50% | Hypotonia and motor delay will resolve in most cases if treatment begins prior to neurological injury [1,10-13]. |
| Benefits of early identification | SOME benefits to family and society | 60% | Genetic counseling and identification of at-risk family members is available [11]. |
| Prevention of mortality | Yes | 55% | Acute episodes of metabolic decompensation are life-threatening events [1,3]. |
| Confirmation of diagnosis | Limited availability | 54% | Plasma acylcarnitines (~20 labs in the US.), urine organic acids may be informative. DNA testing is available on a research basis. 3MCC activity in fibroblasts or leukocytes is the more definitive test [1,12]. |
| Acute management | Limited availability | 57% | Glucose and correction of acidosis are driven by laboratory abnormalities. Care coordination requires metabolic physicians who are of limited availability [1,10-13]. |
| Simplicity of therapy | Periodic involvement of specialist | 46% | Dietary management and supplementation require metabolic disease physicians who are in limited supply [11]. |

**3-Methylcrotonylglycinuria**

**(3-methylcrotonyl-CoA carboxylase deficiency)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1355 /2100 | % of max score | 65% |
| Rank: | 0.76 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

The natural history of 3-MCC has been driven by the clinical ascertainment of patients presenting with severe acute episodes. However, since newborn screening with MS/MS began, many individuals have been identified with the analytes associated with the condition but without apparent clinical manifestations. This situation includes cases where the abnormal metabolites found in the neonatal blood spot were of maternal origin, usually biochemically affected but symptom-free subjects. All elements being considered, it is in the best interest of newborns affected with 3-MCC that the condition be identified in all cases. 3-MCC was therefore included in the core screening panel with the expectation that long-term follow up will lead to a better understanding of this condition and its clinical significance.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| 4 | Steen C et al. Metabolic stroke in isolated 3-methylcrotonyl-CoA carboxylase deficiency. Eur J Pediatr 1999;158:730-3. |
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| 6 | Millington DS, Kodo N, Norwood DL, Roe CR. Tandem mass spectrometry: A new method for acycarnitine profiling with potential for neonatal screening for inborn errors of metabolism. J Inherit Metab Dis 1990;13:321. |
| 7 | Chace DH et al. Use of mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem 2003;49:1797-1798. |
| 8 | National Newborn Screening and Genetics Resource Center. Current newborn conditions by state (as of 07-05-04), http://genes-r-us.uthscsa.edu/. |
| 9 | Zschocke J et al. Progressive infantile neurodegeneration caused by 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency: a novel inborn error of branched-chain fatty acid and isoleucine metabolism. Pediatr Res 2000;48:852-855. |
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| 11 | Seashore MR. The organic acidemias: an overview. Gene Reviews (as of 12-9-03), www.geneclinics.org. |
| 12 | Baumgartner MR et al. The molecular bases of 3-methylcrotonyl-CoA-carboxylase deficiency. J Clin Invest 2001;107:495-504. |
| 13 | Nyhan WL, Ozand PT. 3-Methylcrotonyl-CoA carboxylase deficiency. In: Nyhan WL, Ozand PT (eds). Atlas of Metabolic Diseases. Chapman & Hall, London, 1998;53-56. |

| CONDITION | Beta-ketothiolase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | No clear ethnic differences; perhaps higher in Tunisia [1]. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 20 of 51 states, 30% of annual births (August 2004) |

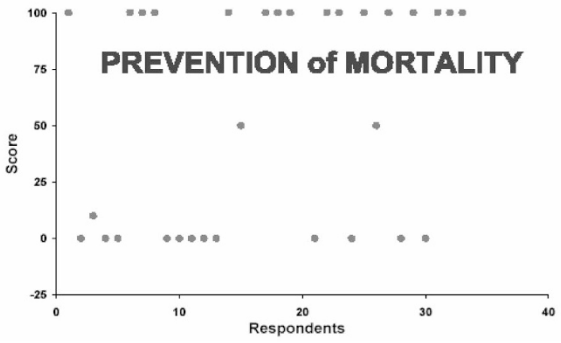
| Responses: | 33 | Valid scores: | 558 | 94% | PubMed references (August 2004) | 434 |
|---|---|---|---|---|---|---|

| Gene | *ACAT1* | Locus | *11q22.3-q23.1* | OMIM | *203750* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 7% | Rare; no population data available. Perhaps higher in Tunisia [1,2]. |
| Phenotype at birth | Almost Never | 88% | Not apparent in neonates [2,3,6-8]. |
| Burden if untreated | Severe | 75% | Variable outcomes ranging from normal development without metabolic episodes to severe retardation and death following a first episode [2,3,6,7]. Mental retardation or ataxia in 28% [2,6,8]. |
| The test | | | |
| Screening test | Yes | 79% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Reported in 1990 [9,10]. |
| Doable in DBS or by physical method | Yes | 88% | Allelic heterogeneity limits molecular second tier tests [2,3,11]. |
| High throughput | Yes | 77% | Up to 500-1000 tests per day [10]. |
| Overall cost <$1 | <$1/test | 57% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [12]. |
| Multiple analytes | Yes | 67% | C5:1 tiglylcarnitine and C5-OH elevated [10,11]. |
| Secondary targets | Yes | 55% | 2M3HBA, 3MGL, ?3MCG, ?MG [2,6,11,12]. |
| Multiplex platform | Yes | 61% | For comprehensive review see [10]. |
| The treatment | | | |
| Availability & cost | Limited availability | 69% | Acute management of ketoacidosis with IV glucose and bicarbonate. Avoidance of fasting and of protein rich and ketogenic diets and stresses [2,3,14,15]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 57% | Early diagnosis and treatment prevents abnormal development [2,3,7,14]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 57% | Significant prevention of mortality [2,3,7]. |
| Benefits of early identification | Some benefits to family and society | 65% | Genetic counseling, identification of relatives, prevention of costs for care of episodes, dismissal of abuse allegations [3,15]. |
| Prevention of mortality | Yes (lack of consensus) (*) | 55% | Significant prevention of mortality [2,6]. |
| Confirmation of diagnosis | Limited availability | 50% | Plasma AC (~20 labs in the US) urine OA (>50 labs in the US) [16]. Enzyme assay to confirm is of very limited availability. |
| Acute management | Limited availability | 61% | Well established emergency protocols. Invasive methods not usually needed [2,17]. |
| Simplicity of therapy | Periodic involvement of specialist (lack of consensus) (*) | 45% | No special food or orphan drugs [2,3]. |

**Beta-ketothiolase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page





**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1282 /2100 | % of max score | 61% |
| Rank: | 0.67 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Fewer than 50 cases of beta-ketothiolase deficiency have been described. The phenotype is quite variable.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| 2 | Mitchell GA et al. Inborn errors of ketone body metabolism. In: Scriver CR et al (eds) The Metabolic and Molecular Bases of Inherited Disease, 8th ed. McGraw-Hill, New York, 2001;2327-56. |
| 3 | Fukao T. Beta-ketothiolase deficiency. Orphanet web site. (as of 09-2004), http://www.orpha.net/data/patho/GB/uk-T2.pdf |
| 4 | Keating JP et al. Hyperglycinemia with ketosis with defect in isoleucine metabolism: A preliminary report. Pediatrics 1972;50:890. |
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| 14 | Saudubray JM et al. Hyperketotic states due to inherited defects of ketolysis. Enzyme 1987;38:80. |
| 15 | Seashore MR. The organic acidemias: an overview. Gene Reviews (as of 12-9-03), www.geneclinics.org |
| 16 | Gene Tests Laboratory Directory, http://www.geneclinics.org/; or UCSD Biochemical Genetics Test List, http://biochemgen.ucsd.edu/ |
| 17 | Dixon MA et al. Intercurrent illness in inborn errors of metabolism. Arch Dis Child 1992;67:1387. |

| CONDITION | Glutaric acidemia type I |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | Panethnic; much more common in Old Order Amish and Island Lake Indians in Canada. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 21 of 51 states, 33% of annual births (August 2004) |

| Responses: | 58 | Valid scores: | 1,012 | 97% | PubMed references (August 2004) | 42 |
|---|---|---|---|---|---|---|

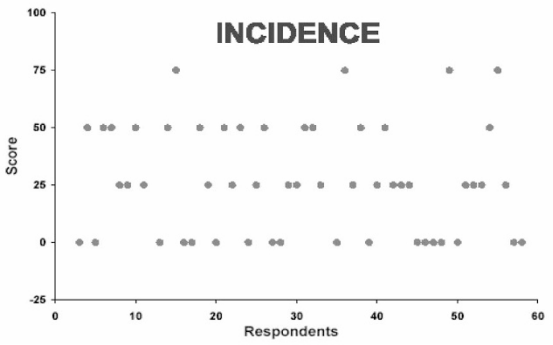
| Gene | *GCDH* | Locus | *19p13.2* | OMIM | *231670* |
|---|---|---|---|---|---|

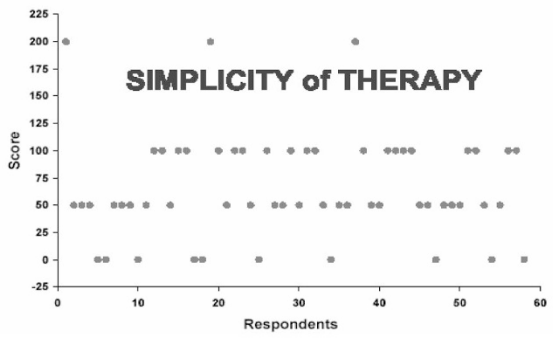
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 27% | 1:50,000 [1,2]; carrier frequency of 1:10 in Old Order Amish [3]. |
| Phenotype at birth | Almost never | 89% | Macrocephaly may be present at birth but often goes unrecognized. Most present in first 6 - 18 months following a respiratory or gastrointestinal illness [2,4,5]. |
| Burden if untreated | Profound | 92% | Acute encephalopathic episode leading to neurological dysfunction and death in first decade for those who become symptomatic [5,6]. |
| The test | | | |
| Screening test | Yes | 94% | MS/MS [7,8]. DNA testing in high incidence populations [9]. |
| Doable in DBS or by physical method | Yes | 100% | Yes [7,8]. |
| High throughput | Yes | 89% | Up to 500-1,000 specimens per day [8]. |
| Overall cost <$1 | <$1/test | 61% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [10]. |
| Multiple analytes | Yes | 79% | C5 dicarboxylic acylcarnitine is increased; C5DC:C16 often increased [8]. |
| Secondary targets | Yes | 71% | GA-II [8]. |
| Multiplex platform | Yes | 81% | For comprehensive review, see [8]. |
| The treatment | | | |
| Availability & cost | Limited availability | 64% | Metabolic physicians for L-carnitine supplementation and aggressive management of intercurent illnesses [2,5]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 44% | Striatal degeneration is avoided in significant proportion if treatment is begun before onset of symptoms [5]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 72% | Striatal degeneration is avoided in significant proportion if treatment is begun before onset of symptoms [5]. |
| Benefits of early identification | CLEAR benefits to family and society | 79% | Genetic counseling and prenatal diagnosis are available; identification of other at-risk family members; dismissal of abuse charges [11,12,13]. |
| Prevention of mortality | Yes | 75% | More than 70% develop normally if treated before their first episode [5,6]. |
| Confirmation of diagnosis | Limited availability | 56% | 3-hydroxyglutaric acid is almost always elevated in plasma (serum) and urine. Assays for glutaryl CoA-dehydrogenase are available, as is diagnosis by mutation analysis. [14,15]. |
| Acute management | Limited availability | 54% | Well established emergency protocols [5,11]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 33% | Regular involvement with metabolic physicians, particularly with intercurrent illnesses. [2,5]. |

**Glutaric acidemia type I**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1435 /2100 | % of max score | 68% |
| Rank: | 0.83 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

GA-I is likely under diagnosed. Not all individuals within families with GA-1 are similarly clinically affected. A metabolic specialist should be involved with the management of GA-I patients at all times.

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| CONDITION | Isobutyryl-CoA dehydrogenase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | No known ethnic variability. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 17 of 51 states, 28% of annual births (August 2004) |

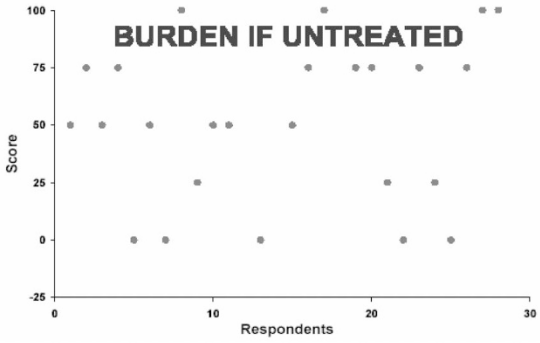
| Responses: | 28 | Valid scores: | 467 | 93% | PubMed references (August 2004) | 23 |
|---|---|---|---|---|---|---|

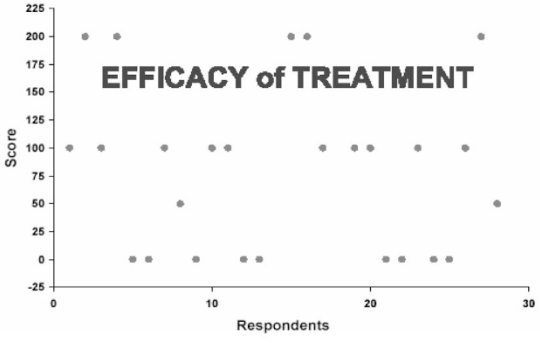
| Gene | *ACAD8* | Locus | *11q25* | OMIM | *604773* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 8% | Incidence not known; very rare [1,4,5,6]. |
| Phenotype at birth | Almost never | 92% | Cardiomyopathy due to carnitine deficiency presents later. Patients identified early are asymptomatic [4,5,6]. |
| Burden if untreated | Moderate (*) | 95% | Natural history not known. |
| The test | | | |
| Screening test | Yes | 81% | MS/MS first reported in 1990 (4,5,7). |
| Doable in DBS or by physical method | Yes | 96% | Yes [8]. |
| High throughput | Yes | 85% | Up to 500-1000 tests per day [8]. |
| Overall cost <$1 | <$1/test | 54% | Likely to be done by MS/MS that is available in ~20 laboratories in the US [9]. |
| Multiple analytes | Yes | 69% | C4 butyrylcarnitine. |
| Secondary targets | Yes | 60% | SCAD. |
| Multiplex platform | Yes | 67% | Yes [4,8]. |
| The treatment | | | |
| Availability & cost | Limited availability | 60% | Carnitine therapy has benefited some patients [6]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (*) | 40% | Carnitine therapy has benefited some patients [6]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 40% | Carnitine therapy has benefited some patients [6]. |
| Benefits of early identification | SOME benefits to family and society | 52% | Genetic counseling and prenatal diagnosis are available [4,5]. |
| Prevention of mortality | No | 37% | Not known. |
| Confirmation of diagnosis | Limited availability | 43% | Plasma acylcarnitines (~20 labs in the US) [10]. |
| Acute management | Only in a few centers | 39% | Experienced metabolic physicians are of very limited availability [3]. |
| Simplicity of therapy | Regular involvement of specialist | 34% | Care coordination by an experienced metabolic disease physician is needed [1]. |

**Isobutyryl-CoA dehydrogenase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1134 /2100 | % of max score | 54% |
| Rank: | 0.42 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Fewer than 10 cases have been described. This is a clinically significant condition detected by acylcarnitine profiling to be included in the differential diagnosis of primary targets.

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| | |
|---|---|
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| CONDITION | Isovaleric Acidemia (isovaleryl-CoA dehydrogenase deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | No apparent ethnic variability. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

| Responses: | 53 | Valid scores: | 930 | 97% | PubMed references (August 2004) | 123 |
|---|---|---|---|---|---|---|

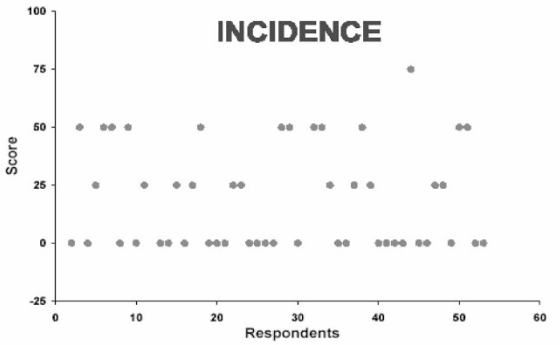
| Gene | *IVA* | Locus | *15q14-q15* | OMIM | *243500* |
|---|---|---|---|---|---|

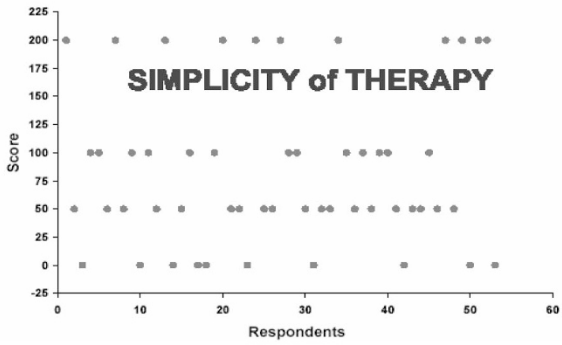
| SURVEY SCORES | | | |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | **LITERATURE AND WEB-BASED EVIDENCE** [References] |
| The condition | | | |
| Incidence | <1:100,000 (lack of consensus) (*) | 19% | First reported in 1966, incidence in the US is between 1:62,500-250,000 [1-3]. |
| Phenotype at birth | Almost never | 83% | Acute onset in the first days or weeks of life is relatively common, but occurs rarely in the first 48 hours; a milder phenotype has recently been described [4]. |
| Burden if untreated | Severe | 84% | Developmental delay, failure to thrive, and hypotonia. Significant mortality in classic cases if acute episode is not treated aggressively [1,3,5]. |
| The test | | | |
| Screening test | Yes | 98% | MS/MS [7-9]. |
| Doable in DBS or by physical method | Yes | 98% | Yes [3,7-9]. |
| High throughput | Yes | 88% | Up to 500-1000 tests per day [3]. |
| Overall cost <$1 | <$1/test | 58% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [10]. |
| Multiple analytes | Yes | 76% | Isolated elevation of C5-carnitine (representing primarily isovalerylcarnitine in IVA) [7,9]. |
| Secondary targets | Yes | 65% | 2MBG (SBCAD deficiency) [7,8]. |
| Multiplex platform | Yes | 71% | Yes [3]. |
| The treatment | | | |
| Availability & cost | Limited availability | 70% | Dietary management with low protein or selective leucine restriction. L-carnitine and/or glycine supplementation [1,5,13]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 55% | High likelihood of complete prevention of morbidity [11-13]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 84% | Treatment prior to irreversible neurologic damage prevents recurrence of symptoms in most cases [11,12]. |
| Benefits of early identification | CLEAR benefits to family and society | 87% | Genetic counseling and identification of at-risk family members is available; prevention of costs for care of catastrophic episodes, dismissal of abuse charges, prenatal diagnosis is possible [14,6]. |
| Prevention of mortality | Yes | 91% | Acute episodes of metabolic decompensation are life-threatening events [4,5,15]. |
| Confirmation of diagnosis | Limited availability | 62% | Urine acylglycines, urine organic acids, and plasma acylcarnitines usually sufficient to confirm diagnosis. Cell-based in vitro studies in fibroblast cultures and DNA analysis for common mutation (A282V) can be helpful; specific enzyme assay and gene sequencing available on a research basis only [14,17]. |
| Acute management | Limited availability | 56% | Well-established emergency protocols [4,5,17]. |
| Simplicity of therapy | Periodic involvement of specialist (lack of consensus) (*) | 42% | Metabolic physicians are required for dietary management and care coordination in collaboration with PCP [5,18]. |

**Isovaleric acidemia**

**(isovaleryl-CoA dehydrogenase deficiency)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1493 /2100 | % of max score | 71% |
| Rank: | 0.89 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

The incidence and natural history of isovaleric acidemia are well understood. This condition meets the criteria for inclusion in the uniform panel. The test is sensitive and specific, treatment is available to reduce morbidity and mortality.

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| CONDITION | Malonic acidemia |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | No known ethnic variability. |
| SCREENING METHOD(S) | tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 10 of 51 states, 13% of annual births (August 2004) |

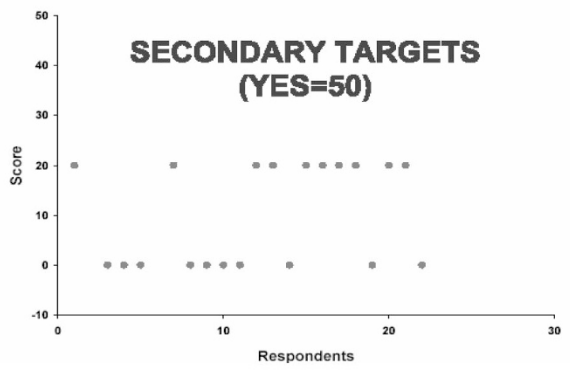
| Responses: | 22 | Valid scores: | 378 | 95% | PubMed references (August 2004) | 111 |
|---|---|---|---|---|---|---|

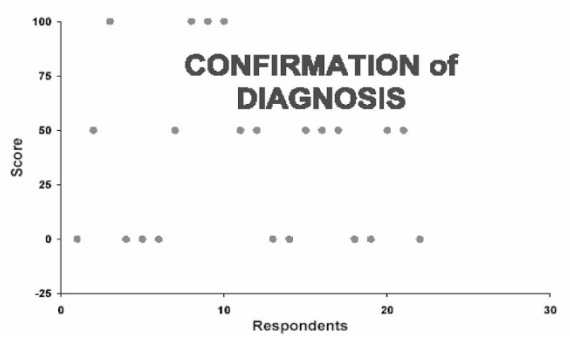
| Gene | *MLYCD* | Locus | *16q24* | OMIM | *248360* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | **LITERATURE AND WEB-BASED EVIDENCE** [References] |
| The condition | | | |
| Incidence | <1:100,000 | 5% | Not known; very rare [1]. |
| Phenotype at birth | Almost never | 89% | At least one has presented as neonate; most are later [1-6]. |
| Burden if untreated | Severe | 71% | Mortality and long term disability are high [1-6]. |
| The test | | | |
| Screening test | Yes | 76% | MS/MS first reported in 1990 [7]. |
| Doable in DBS or by physical method | Yes | 80% | Yes [8,9]. |
| High throughput | Yes | 70% | Up to 500-1000 tests per day [10]. |
| Overall cost <$1 | <$1/test | 55% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [11]. |
| Multiple analytes | Yes | 55% | C3DC Malonylcarnitine, benzoylcarnitine, C3 propionylcarnitine [10]. |
| Secondary targets | No (lack of consensus) (*) | 50% | Propionic acidemia, MMA [10]. |
| Multiplex platform | Yes | 70% | Yes, see [10] for comprehensive review. |
| The treatment | | | |
| Availability & cost | Limited availability | 64% | Carnitine supplementation and dietary management [1,2]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 26% | Efficacy is not yet known; some partial improvements in phenotypes are reported [1,12,14]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 50% | Efficacy is not yet known; some partial improvements in phenotypes are reported [1,12,14]. |
| Benefits of early identification | SOME benefits to family and society | 70% | Genetic counseling is available and prenatal diagnosis is feasible [13]. |
| Prevention of mortality | Yes | 52% | Unknown but likely to improve mortality [1,13,14]. |
| Confirmation of diagnosis | Only a few centers (lack of consensus) (*) | 39% | Plasma acylcarnitines (~20 labs in the US) [15-18]. Requires enzymology and mutation testing that are available in only a few centers. |
| Acute management | Limited availability | 56% | Experienced metabolic physicians are of very limited availability [13]. |
| Simplicity of therapy | Regular involvement of specialist | 30% | Dietary management and supportive care requires routine involvement of specialists [13]. |

**Malonic acidemia**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1143 /2100 | % of max score | 54% |
| Rank: | 0.45 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Fewer than 20 patients have been described. This is a clinically significant condition detected by acylcarnitine profiling.

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| | |
|---|---|
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| CONDITION | Methylmalonic acidemia (complementation groups: Cbl A and Cbl B) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | Cases reported worldwide, no ethnic differences. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

| Responses: | 46 | Valid scores: | 815 | 98% | PubMed references (August 2004) | 561 |
|---|---|---|---|---|---|---|

| Gene | *MMAA MMAB* | Locus | *4q31.1-q31.2 12Q24* | OMIM | *251100; 251110* |
|---|---|---|---|---|---|

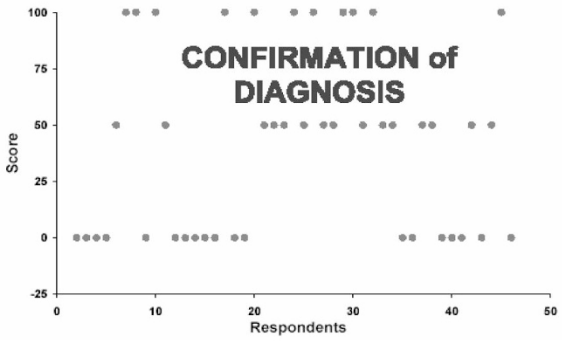
**SURVEY SCORES**

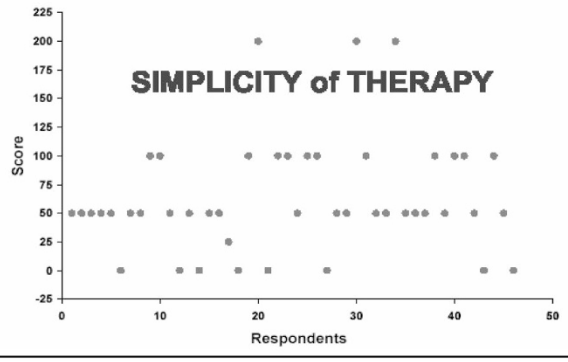
| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 14% | Estimated at 1:48,000 live births for all complementation groups [1,2]. |
| Phenotype at birth | Almost never | 85% | 30-40% of cases present with overwhelming illness (ketoacidosis, coma) in the first week of life. Late onset (>1 yr) in ~10% of cases [1,3,4]. |
| Burden if untreated | Profound | 92% | Developmental delay (30%), failure to thrive (80%), and hypotonia (40-50%). Significant mortality during acute episodes [1,4-10]. |
| The test | | | |
| Screening test | Yes | 87% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Propionylcarnitine has a relatively high rate of false positives. False negatives have been reported [12,13]. |
| Doable in DBS or by physical method | Yes | 89% | Yes [13]. |
| High throughput | Yes | 75% | Up to 500-1000 tests per day [12,13]. |
| Overall cost <$1 | No (>$1/test) | 50% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [13]. |
| Multiple analytes | Yes | 69% | C3 and ratios to other species (C2, C16), methylmalonylcarnitine (C3-DC) inconsistently detected [12,13]. |
| Secondary targets | Yes | 53% | Other complementation groups [12,13]. |
| Multiplex platform | Yes | 62% | Yes [13]. |
| The treatment | | | |
| Availability & cost | Limited availability | 65% | Cobalamin supplementation, L-carnitine, gut sterilization, low protein diets. Liver transplantation in a few cases [1,4,5,10,11,14]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 46% | Reverses clinical and biochemical abnormalities in most cases with CblA. In CblB, 1/3 do well, 1/3 have deficits, and 1/3 die [1,2,5]. |
| Benefits of early intervention | Clear evidence that early intervention optimizes individual outcome | 77% | Reverses clinical and biochemical abnormalities in 90% of cases with CblA. In CblB, 1/3 do well, 1/3 have deficits, and 1/3 die [1,2,5]. |
| Benefits of early identification | Clear benefits to family and society | 80% | Genetic counseling and prenatal diagnosis are available. Possible prenatal therapy [16,17]. |
| Prevention of mortality | Yes | 89% | Acute episodes of metabolic decompensation are life-threatening events [1,9]. |
| Confirmation of diagnosis | Limited availability (lack of consensus) (*) | 41% | Plasma acylcarnitines (~20 labs in the US.), urine organic acids, plasma aminoacids. Complementation studies in skin fibroblasts [1,14,15]. |
| Acute management | Limited availability | 57% | Well established emergency protocols [1,14,16]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 32% | Metabolic physicians and other specialist are required on an ongoing basis [14]. |

**Methylmalonic acidemia**

**(complementation groups: Cbl A and Cbl B)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**Methylmalonic acidemia**

**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1343 /2100 | % of max score | 64% |
| Rank: | 0.73 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

The incidence and natural history of methylmalonic acidemias are well understood. Fewer than 100 patients have been identified. Methylmalonic acidemias (CblA and CblB complementation groups) meet the criteria for inclusion in the uniform panel. The test is adequately sensitive and specific, treatment is available to reduce morbidity and mortality.

**REFERENCES AND WEB SITES**


| | |
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| 14 | Seashore MR. The organic acidemias: an overview. Gene Reviews (as of 12-9-03), www.geneclinics.org |
| 15 | Ledley FD et al. Mutations in mut methylmalonic acidemia: clinical and enzymatic correlations. Hum Mutat 1997:9:1-6. |
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| 17 | Sweetman L. Prenatal diagnosis of the organic acidurias. J Inher Metab Dis 1984;7(suppl 1):18-22. |

| CONDITION | Methylmalonic acidemia (complementation groups: Cbl C and Cbl D) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | Cases reported worldwide, no ethnic differences. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

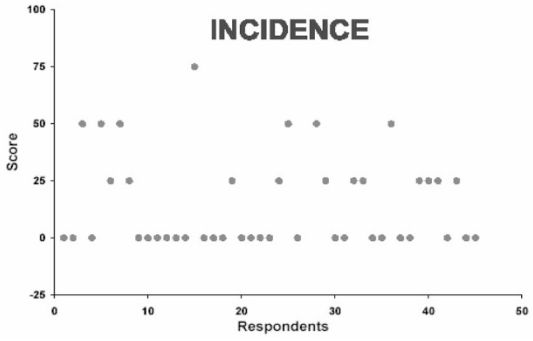
| Responses: | 45 | Valid scores: | 775 | 96% | PubMed references (August 2004) | 61 |
|---|---|---|---|---|---|---|

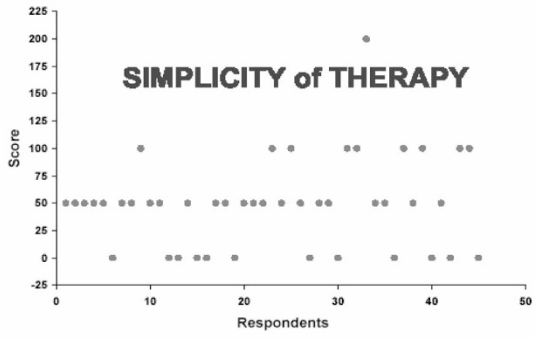
| Gene | *CBLC CBLD* | Locus | *19Q13.2* | OMIM | *277400; 277410* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 (*) | 15% | Estimated at 1:48,000 live births for all complementation groups. Cbl D is an extremely rare condition [1,2]. |
| Phenotype at birth | <25% of cases | 83% | 80-90% of cases present in the first year of life, including overwhelming illness in the first week of life [1,3,4]. |
| Burden if untreated | Severe | 89% | Developmental delay, failure to thrive, megaloblastic anemia, seizures [3-14]. |
| The test | | | |
| Screening test | Yes | 71% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Propionylcarnitine has a relatively high rate of false positives. False negatives have been reported [15,16]. |
| Doable in DBS or by physical method | Yes | 84% | Yes [16]. |
| High throughput | Yes | 71% | Up to 500-1000 tests per day [16]. |
| Overall cost <$1 | No (>$1/test) | 48% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT,MI,NY,RI,VA,WA) [17]. |
| Multiple analytes | No | 63% | C3 and ratios to other species (C2, C16), methylmalonylcarnitine (C3-DC) inconsistently detected. [15,16] Homocystine elevated and methionine is low but they may not be assessed. |
| Secondary targets | Yes | 49% | Other complementation groups [15,16]. |
| Multiplex platform | Yes | 53% | Yes [16]. |
| The treatment | | | |
| Availability & cost | Limited availability | 64% | Cobalamin supplementation, L-carnitine, antibiotics, low protein diets. [4,5,9-13]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 31% | Response to treatment is often unsatisfactory [2,9-13]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 58% | Outcome varies with complementation group and age of onset of symptoms [1,9-13]. |
| Benefits of early identification | CLEAR benefits to family and society | 76% | Genetic counseling and prenatal diagnosis are available [19,20]. |
| Prevention of mortality | Yes | 74% | Acute episodes of metabolic decompensation are life-threatening events [1,9,18]. |
| Confirmation of diagnosis | Only a few centers | 38% | Plasma acylcarnitines (~20 labs in the US), urine organic acids, plasma amino acids. Complementation studies in skin fibroblasts [17,19,20]. |
| Acute management | Limited availability | 51% | Well established emergency protocols [2,19]. |
| Simplicity of therapy | Regular involvement of specialist (*) | 25% | Metabolic physicians and other specialists are required on an ongoing basis [18]. Transplantation in limited centers. |

**Methylmalonic acidemia**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1166 /2100 | % of max score | 56% |
| Rank: | 0.49 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Methylmalonic acidemias (CblC and CblD complementation groups) meet the criteria for inclusion in the report only group because they are required for the differential diagnosis of other conditions included in the uniform panel. CblC can be missed on newborn screening due to low metabolite levels in some cases.

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20. Sweetman L. Prenatal Diagnosis of the Organic Acidurias. J Inher Metab Dis 1984;7(suppl 1):18-22.

| CONDITION | Methylmalonic acidemia (methylmalonyl-CoA mutase deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

| Responses: | 60 | Valid scores: | 1,055 | 98% | PubMed references (August 2004) | 366 |
|---|---|---|---|---|---|---|

| Gene | *MUT* | Locus | *6p21* | OMIM | *251000* |
|---|---|---|---|---|---|

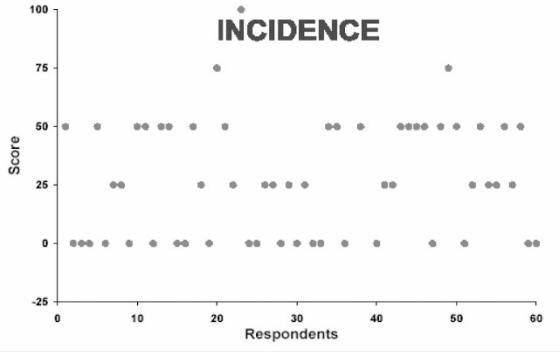
**SURVEY SCORES**

| Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 28% | Estimated at 1:48,000 live births for all complementation groups [1]. |
| Phenotype at birth | Almost never | 81% | 80% of mut° patients present in first week of life while mut⁻ cases present after first month. Rare cases present later in life. [2,3,4,5]. Minority of cases have dysmorphisms that may be apparent at birth. |
| Burden if untreated | Profound | 96% | Developmental delay, failure to thrive, and muscular hypotonia. Significant mortality during acute episodes [2-9]. |
| The test | | | |
| Screening test | Yes | 90% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Propionylcarnitine has a relatively high rate of false positives. False negatives have been reported [10,11]. |
| Doable in DBS or by physical method | Yes | 97% | Yes [11]. |
| High throughput | Yes | 86% | Up to 500-1000 tests per day [11]. |
| Overall cost <$1 | <$1/test | 63% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [12]. |
| Multiple analytes | Yes | 77% | C3 and ratios to other species (C2, C16), methylmalonylcarnitine (C3-DC) inconsistently detected [10,11]. |
| Secondary targets | Yes | 54% | Several Cbl complementation groups (Cbl A-H) [10,11]. |
| Multiplex platform | Yes | 67% | Yes [11]. |
| The treatment | | | |
| Availability & cost | Limited availability | 58% | Low protein diet, precursor-free formulas, L-carnitine, and antibiotics. Liver or liver/kidney transplantation in a few cases [13-17]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 38% | Outcome varies with complementation group and age of onset of symptoms [14-17]. 60% may still die after treatment. Combined liver-kidney transplantation can correct renal disease and normalize metabolic status. Liver transplantation does not protect against renal complications. Efficacy in preventing late neurological disease is suspect [16,17]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 75% | Outcome varies with type and age of onset of symptoms [14-17]. Combined liver-kidney transplantation for severe cases can correct renal disease and normalize metabolic status [16,17]. |
| Benefits of early identification | CLEAR benefits to family and society | 79% | Genetic counseling and prenatal diagnosis are available [18,19]. |
| Prevention of mortality | Yes | 93% | Acute episodes of metabolic decompensation are life-threatening events [14-17]. |
| Confirmation of diagnosis | Limited availability | 53% | Plasma acylcarnitines (~20 labs in the US.), urine organic acids, plasma amino acids [18]. Complementation studies in skin fibroblasts. DNA testing is available on a research basis, significant allelic heterogeneity [17,19]. |
| Acute management | Limited availability | 51% | Well established emergency protocols [8,13-15,17]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 22% | Metabolic physicians and other specialists are required on an ongoing basis [17]. |

**Methylmalonic acidemia**

**(methylmalonyl-CoA mutase deficiency)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page





**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1358 /2100 | % of max score | 65% |
| Rank: | 0.78 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

The incidence and natural history of methylmalonic acidemia are well understood. This condition meets the criteria for inclusion in the uniform panel. The test is adequately sensitive and specific, treatment is available to reduce morbidity and mortality.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| 20 | Ledley FD, Rosenblatt DS. Mutations in mut methylmalonic acidemia: clinical and enzymatic correlations. Hum Mutat 1997:9:1-6. |

| CONDITION | Holocarboxylase synthetase deficiency (multiple carboxylase deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | No known ethnic variability. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 16 of 51 states, 25% of annual births (August 2004) |

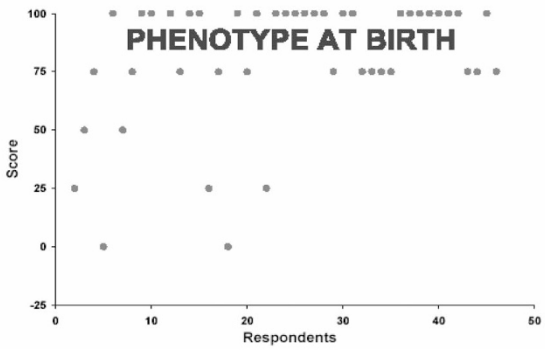
| Responses: | 46 | Valid scores: | 812 | 98% | PubMed references (August 2004) | 155 |
|---|---|---|---|---|---|---|

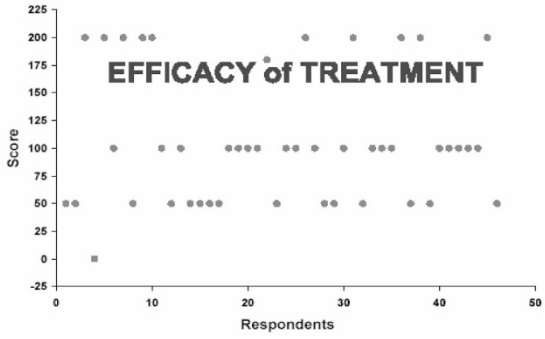
| Gene | *HLCS* | Locus | *21Q22.1* | OMIM | *253270* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | <1:100,000 | 6% | First case described in 1971 [1]. Incidence estimated at 1:87,000 [2-3]. |
| Phenotype at birth | <25% of cases (lack of consensus) (*) | 96% | Most patients present before six weeks of age [4-8]. |
| Burden if untreated | Severe | 91% | Episodes of ketoacidosis evolving in dehydration and coma, skin manifestations, alopecia [4-8]. |
| The test | | | |
| Screening test | Yes | 77% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling [9]. |
| Doable in DBS or by physical method | Yes | 84% | Yes [9]. |
| High throughput | Yes | 75% | Up to 500-1,000 specimens per day [9]. |
| Overall cost <$1 | <$1/test | 52% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [10]. |
| Multiple analytes | Yes | 71% | Propionylcarnitine (and ratios to other species), 3-OH isovalerylcarnitine [9,11]. |
| Secondary targets | Yes | 53% | Single defects of the three carboxylases, biotinidase deficiency [5]. |
| Multiplex platform | Yes | 62% | Yes [9]. |
| The treatment | | | |
| Availability & cost | Widely available | 72% | Biotin treatment is widely available and inexpensive ($100 - $300 per year) [12]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences (lack of consensus) (*) | 53% | High likelihood of complete prevention of morbidity, responsiveness to biotin may vary [5,6,7,13,14,16]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 77% | Treatment prior to irreversible neurologic damage resolves symptoms in most cases [5,6,7,13,14,16]. |
| Benefits of early identification | CLEAR benefits to family and society | 85% | Genetic counseling and prenatal diagnosis are available, prenatal treatment is possible [15,16]. |
| Prevention of mortality | Yes | 93% | Acute episodes of metabolic decompensation are life-threatening events [5,6,7,13,14,16]. |
| Confirmation of diagnosis | Limited availability | 49% | Holocarboxylase synthetase activity assay is of limited availability. Diagnosis is also possible by measuring carboxylase activities with and without added biotin. Molecular testing available but there is considerable allelic heterogeneity [6-8]. |
| Acute management | Limited availability | 54% | Metabolic specialists for initial treatment and monitoring are of limited availability. Well established emergency protocols [18]. |
| Simplicity of therapy | Periodic involvement of specialist | 46% | Metabolic physicians are required for periodic dietary management and care coordination [19]. |

**Holocarboxylase synthetase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1232 /2100 | % of max score | 59% |
| Rank: | 0.6 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

The incidence and natural history of multiple carboxylase deficiency are not well understood. However, this condition meets the criteria for inclusion in the uniform panel because the MS/MS test is sensitive and specific, and treatment is widely available to prevent morbidity and mortality. Of note, the availability of treatment was perceived differently by all respondents as compared to experts who considered biotin treatment to be relatively simple. It is assumed that the perception of treatment complexity was based on the need for acute management in a significant proportion of early-onset cases.

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| CONDITION | Propionic acidemia (propionyl-CoA carboxylase deficiency) |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of organic acid metabolism |
| ETHNICITY | Panethnic; higher in Saudi Arabia and among Greenland's Inuits. |
| SCREENING METHOD(S) | Tandem mass spectrometry (MS/MS) |
| NBS STATUS in the US | Screened for in 22 of 51 states, 35% of annual births (August 2004) |

| Responses: | 68 |
|---|---|

| Valid scores: | 1,194 | 98% |
|---|---|---|

| PubMed references (August 2004) | 238 |
|---|---|

| Gene | *PCCA PCCB* |
|---|---|

| Locus | *13q32 3q21-q22* |
|---|---|

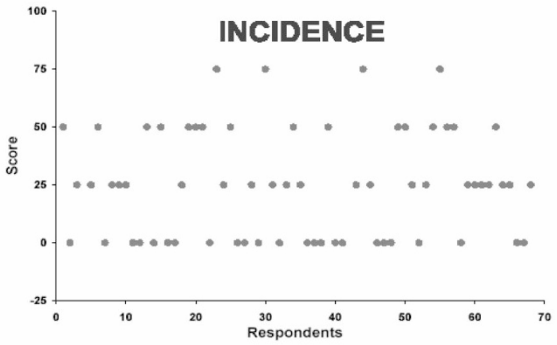
| OMIM | *232000 232050* |
|---|---|

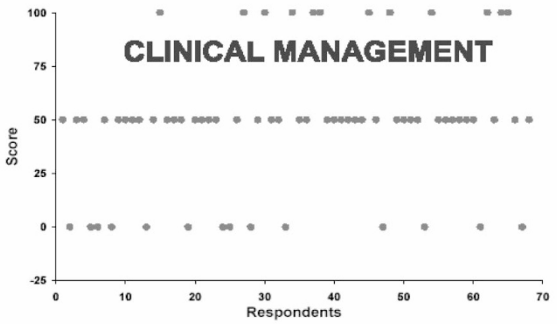
| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 25% | First reported in the 1960's, hundreds of cases diagnosed worldwide. Incidence estimated at 1:100,000; 1:2,000-5,000 in Saudi Arabia and 1:1,000 in Inuits from Greenland [1,2,3]. |
| Phenotype at birth | <25% of cases | 79% | 25% of cases present neonatally with severe metabolic acidosis [4]. |
| Burden if untreated | Profound | 97% | Metabolic acidosis and hyperammonemia leading to severe neurological damage, coma and death. Cases with milder phenotypes are being identified in newborn screening [5,6,7,8]. |
| The test | | | |
| Screening test | Yes | 90% | MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Propionylcarnitine has a relatively high rate of false positives. False negatives have been reported [9,10]. |
| Doable in DBS or by physical method | Yes | 94% | Yes [10]. |
| High throughput | Yes | 86% | Up to 500-1000 tests per day [9]. |
| Overall cost <$1 | Clear benefits to family and society | 59% | Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [11]. |
| Multiple analytes | Yes | 75% | C3 and ratios to other species (C2, C16) [9]. |
| Secondary targets | Yes | 57% | MCD, MMA (MUT, Cbl A-D) [9]. |
| Multiplex platform | Yes | 66% | Yes [9]. |
| The treatment | | | |
| Availability & cost | Limited availability | 57% | Dietary management with low protein or selective restrictions. L-carnitine is useful. Metabolic physicians for dietary management are of very limited availability [12,13,15]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 38% | Even when treated, developmental delay, seizures and other neurological complications, as well as bone marrow suppression are common [4,7,14]. |
| Benefits of early intervention | CLEAR evidence that early intervention optimizes individual outcome | 76% | Morbidity prevention is rarely complete [4,7,14]. |
| Benefits of early identification | CLEAR benefits to family and society | 79% | Genetic counseling and prenatal diagnosis are available. [16,17]. |
| Prevention of mortality | Yes | 89% | Acute episodes of metabolic decompensation are life-threatening events [5,6,7,8]. |
| Confirmation of diagnosis | Limited availability | 54% | Plasma acylcarnitines (~20 labs in the US.), urine organic acids, plasma amino acids [18]. Enzyme assay of propionyl CoA carboxylase activity is available in few laboratories. DNA testing is available on a research basis, significant allelic heterogeneity [19]. |
| Acute management | Limited availability (lack of consensus) (*) | 49% | Well established emergency protocols [2,6]. |
| Simplicity of therapy | Regular involvement of specialist | 17% | Metabolic physicians are required for dietary management and care coordination. |

**Propionic acidemia**

**(propionyl-CoA carboxylase deficiency)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | MS/MS |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1333 /2100 | % of max score | 63% |
| Rank: | 0.72 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

The incidence and natural history of propionic acidemia are well understood. This condition meets the criteria for inclusion in the uniform panel. The test is adequately sensitive and specific, treatment is available to reduce morbidity and mortality

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# HEMATOLOGY/HEMOGLOBINOPATHY

| CONDITION | Sickle cell anemia (Hb SS disease) |
|---|---|
| TYPE of DISORDER | Hemoglobinopathy |
| ETHNICITY | Most common among those of African ancestry > Mediterranean, Caribbean, South and Central America, Arabian ancestry > Northern European ancestry [3]. |
| SCREENING METHOD(S) | HPLC and Isoelectrofocusing |
| NBS STATUS in the US | Screened for in 49 of 51 states, 99% of annual births (August 2004) |

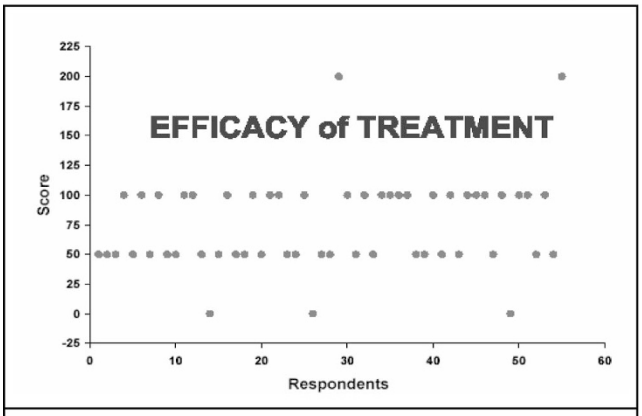
| Responses: | 55 | Valid scores: | 834 | 84% | PubMed references (August 2004): | 14,447 |
|---|---|---|---|---|---|---|

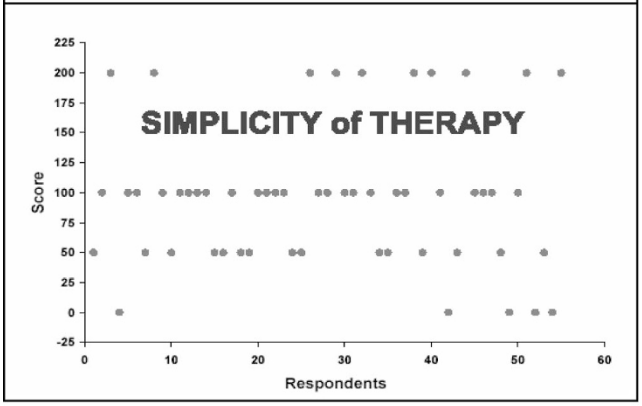
| Gene | *HBB* | Locus | *11p15.5* | OMIM | *603903; 141900* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | >1:5,000 | 80% | 1:3,721 in US newborn screens in 28,149,621 newborns [1]. |
| Phenotype at birth | Almost never | 94% | Although clinical manifestations are very heterogeneous, presentation is usually in the first 2 years of life [2]. |
| Burden if untreated | Profound | 85% | Hemolysis, vascular occlusion & tissue ischemia may lead to injury to every organ system. Serious complications in early childhood include infection, vaso-occlusive pain crises, acute chest syndrome, acute splenic sequestration, aplastic anemia and stroke (10% of children) [3-7]. |
| The test | | | |
| Screening test | Yes | 98% | IEF or HPLC in most states [8,9]. DNA analysis can be done on dried blood spots. |
| Doable in DBS or by physical method | Yes | 99% | Yes, see [8,9]. |
| High throughput | Yes | 98% | Yes, see [8,9]. |
| Overall cost <$1 | <$1/test | 66% | Cost per test varies with reporting practices for variant hemoglobinopathies [10]. |
| Multiple analytes | Yes | 70% | Yes, see [8,9]. |
| Secondary targets | Yes | 62% | Yes, see [8,9]. |
| Multiplex platform | Yes | 45% | Yes, see [8,9]. |
| The treatment | | | |
| Availability & cost | Widely available | 87% | Pediatric hematologists with experience in hemoglobinopathies are moderately available. Prophylactic medications, health maintenance visits and coordination of care are critical [11-13]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (lack of consensus) (*) | 38% | Immunizations prevent some infections. Conjugated pneumococcal vaccine and/or penicillin prophylaxis prevents 80% of life threatening episodes of strep pneumoniae sepsis [11-13]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 66% | Immunizations prevent some infections. Conjugated pneumococcal vaccine and/or penicillin prophylaxis prevents 80% of life-threatening episodes of strep. pneumoniae sepsis [11-14]. |
| Benefits of early identification | CLEAR benefits to family and society | 85% | Enables detection in relatives. Genetic counseling available [15,16]. |
| Prevention of mortality | Yes | 88% | Conjugated pneumococcal vaccine and/or penicillin prophylaxis prevents 80% of life threatening episodes of strep, pneumoniae sepsis [12,14,15] and red cell transfusions prevent stroke [14]. |
| Confirmation of diagnosis | Widely available | 99% | Confirmation with an alternative method (HPLC, complementary electrophoretic methods, and DNA is done on the DBS or a separate specimen [5,6]. |
| Acute management | Widely available | 89% | Care for fever, acute chest syndrome (ACS), and splenic sequestration is widely available. Some episodes of pain are managed at home. Hydroxyurea can be used to prevent vasoocclusive pain crises and ACS in children [16]. |
| Simplicity of therapy | Periodic involvement of a specialist (lack of consensus) (*) | 48% | Some care is provided at home. Preventive therapies relatively simple. Care coordination is more complex [17-19]. |

**Sickle cell anemia (Hb SS disease)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | HPLC |
| 2ary target of higher scoring condition? | | | No |
| Final score | 1542 /2100 | % of max score | 73% |
| Rank: | 0.94 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Sickle cell anemia (Hb-SS disease) was among the highest scoring conditions in these analyses. Due to its relatively high incidence and inclusion in newborn screening programs for many years, the data on testing, burdens of disease, treatment efficacy and outcome are robust.

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| CONDITION | Hemoglobin SC |
|---|---|
| TYPE of DISORDER | Hemoglobinopathy |
| ETHNICITY | Primarily in population of West African ancestry. |
| SCREENING METHOD(S) | High pressure liquid chromatography (HPLC) or isoelectric focusing (IEF) |
| NBS STATUS in the US | Screened for in 49 of 51 states, 99% of annual births (August 2004) |

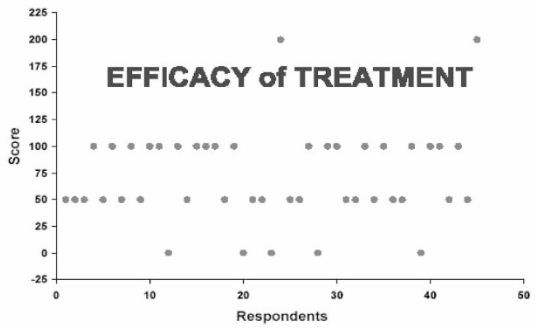
| Responses: | 45 | Valid scores: | 782 | 97% | PubMed references (August 2004): | 1,097 |
|---|---|---|---|---|---|---|

| Gene | *HBB* | Locus | *11p15.5* | OMIM | *603903* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | >1:25,000 | 61% | 1:7,386 in US newborn screens of 28,149,621 newborns reported to the NNSGRC [1]. |
| Phenotype at birth | Almost never | 91% | Never [2, 3]. |
| Burden if untreated | Severe | 65% | Phenotype milder than SCA (HbSS disease) [4]. Among those more severely affected, hemolysis, vascular occlusion & tissue ischemia may lead to injury to in every organ system. Serious complications in early childhood include infection, vaso-occlusive pain crises, acute chest syndrome, acute splenic sequestration, aplastic anemia and stroke (10% of children) [3-6]. |
| The test | | | |
| Screening test | Yes | 98% | Isoelectric focusing (IEF) in most states [7]. Confirmatory screening is usually by extended IEF or citrate agar electrophoresis and DNA testing may be done. [19,20]. |
| Doable in DBS or by physical method | Yes | 98% | Yes, see [7]. |
| High throughput | Yes | 82% | Yes. [7]. |
| Overall cost <$1 | <$1/test | 65% | Per test cost per condition varies with reporting practices for variant hemoglobinopathies [8]. |
| Multiple analytes | Yes | 71% | Yes, see [7]. |
| Secondary targets | Yes | 62% | Yes, see [7]. |
| Multiplex platform | Yes | 49% | Yes, see [7]. |
| The treatment | | | |
| Availability & cost | Widely available | 85% | Pediatric hematologists with experience in hemoglobinopathies are moderately available. Prophylactic medications, health maintenance visits and coordination of care are critical [9-13,19,20]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (lack of consensus) (*) | 36% | Immunizations prevent some infections. Conjugated pneumococcal vaccine and/or penicillin prophylaxis prevents 80% of life threatening episodes of strep pneumoniae sepsis [10-13]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 56% | Immunizations and penicillin prophylaxis prevent some infections and 80% of life-threatening episodes of strep pneumoniae sepsis. Ophthalmologic monitoring detects retinal complications. Monitoring for avascular necrosis of hip allows early intervention [11]. |
| Benefits of early identification | CLEAR benefits to family and society | 81% | Allows for detection in relatives. Genetic counseling available [9]. |
| Prevention of mortality | Yes | 73% | Immunizations and penicillin prophylaxis prevent some infections. Vasoocclusion can lead to typical acute chest syndrome [9, 11,12]. |
| Confirmation of diagnosis | Widely available | 97% | Confirmation with an alternative method (HPLC, complementary electophoretic methods, and DNA) is done on a separate specimen [7]. |
| Acute management | Widely available | 90% | Care for fever, acute chest syndrome (ACS), and splenic sequestration is widely available. Some episodes of pain are managed at home. Hydroxyurea can be used to prevent vasoocclusive pain crises and ACS in children [12,13]. |
| Simplicity of therapy | Primary care, family level (lack of consensus) (*) | 49% | Some care provided at home. Preventive therapies relatively simple. Care coordination is more complex [4, 14-20]. |

**Hemoglobin SC**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page





**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | HPLC |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1453 /2100 | % of max score | 69% |
| Rank: | 0.86 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

Although considerably less common than SCA, Hb-SC disease is detected with all other hemoglobin variants and is a clinically significant condition. Although disease is milder than in SCA, complications such as proliferative retinopathy and osteonecrosis of the hips are progressive. The disease often goes unrecognized until serious complications occur. Both individually and as a group, the sickle cell anemias scored in the top 6 - 13 conditions and are clearly important for newborn screening.

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| CONDITION | Hemoglobin S/beta thalassemia (Hb S-ßthal) |
|---|---|
| TYPE of DISORDER | Hemoglobinopathy |
| ETHNICITY | Hb S is most common among those of African ancestry > Mediterranean, Caribbean, South and Central America, Arabian ancestry > Northern European ancestry [3]. |
| SCREENING METHOD(S) | High pressure liquid chromatography (HPLC) or isoelectric focusing (IEF) |
| NBS STATUS in the US | HbSß+ is screened for in 49 of 51 states, 99% of annual births (August 2004) |

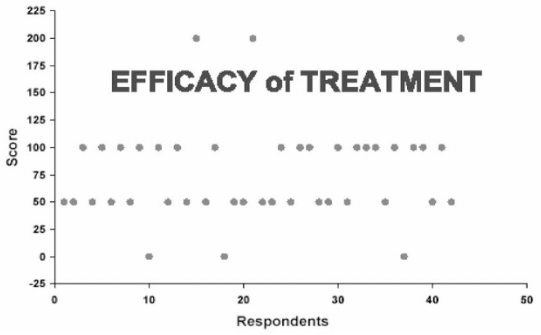
| Responses: | 43 | Valid scores: | 745 | 96% | PubMed references (August 2004): | 478 |
|---|---|---|---|---|---|---|

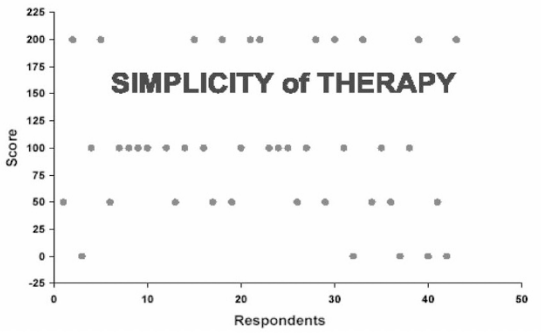
| Gene | *HBA1* | Locus | *11p15.5* | OMIM | *141900* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | >1:50,000 | 55% | 1:18,805 in London, UK [1]. |
| Phenotype at birth | Almost never | 94% | May present in first 1 -2 yrs but depends on the severity of the ß-thal mutations with ß° being similar to SS and ß+ being quite variable. [2, 3]. |
| Burden if untreated | Severe | 69% | Hemolysis, vascular occlusion & tissue ischemia leads to injury to every organ. Catastrophic stroke in as many as 10% of children with ß° [4-6 ]. |
| The test | | | |
| Screening test | Yes | 89% | Isoelectric focusing or HPLC in most states detects HbSß+. Distinguishing Sß° from SS requires family studies or DNA testing. Confirmatory screen usually uses extended IEF and citrate agar electrophoresis [7]. |
| Doable in DBS or by physical method | Yes | 98% | Yes, see [7]. |
| High throughput | Yes | 78% | Yes, see [7]. |
| Overall cost <$1 | <$1/test | 61% | Cost per test varies with reporting practices for variant hemoglobinopathies [8]. |
| Multiple analytes | Yes | 67% | Yes, see [7]. |
| Secondary targets | Yes | 62% | Yes, see [7]. |
| Multiplex platform | Yes | 50% | Yes, see [7]. |
| The treatment | | | |
| Availability & cost | Widely available | 88% | Experienced pediatric hematologists are moderately available. Health maintenance visits and coordination of care are critical. Prophylactic medications may be useful in severe cases [9-13,18]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (lack of consensus) (*) | 39% | Efficacy varies with severity. Immunizations prevent some infections. Conjugated pneumococcal vaccine and/or penicillin prophylaxis prevents 80% of life threatening episodes of strep pneumoniae sepsis [10-14,18]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 58% | Immunizations and penicillin prophylaxis prevent some infections and 80% of life-threatening episodes of strep pneumoniae sepsis. Ophthalmologic monitoring detects retinal complications. Monitoring for avascular necrosis of hip allows early intervention [11]. |
| Benefits of early identification | CLEAR benefits to family and society | 81% | Allows for detection in relatives. Genetic counseling is available [9]. |
| Prevention of mortality | Yes | 79% | Immunizations and penicillin prophylaxis prevent some infections in S/ß° cases. Vasoocclusion can lead to typical acute chest syndrome [9,11,12,16]. |
| Confirmation of diagnosis | Widely available | 96% | Confirmation with an alternative method (HPLC, complementary electophoretic methods, and DNA) is done on a separate specimen. Distinguishing S/ß° cases from SS cases may require family studies and/or DNA studies if done prior to age 6 months [7,9]. |
| Acute management | Widely available | 88% | Care for fever, acute chest syndrome (ACS), and splenic sequestration is widely available. Some episodes of pain are managed at home. Hydroxyurea can be used to prevent vasoocclusive pain crises and ACS in children. [12,13]. |
| Simplicity of therapy | Periodic involvement of a specialist (lack of consensus) (*) | 51% | Some care provided at home. Preventive therapies relatively simple. Care coordination is more complex [4,14-20]. |

**Hemoglobin S/beta thalassemia (Hb S-ßthal)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | HPLC |
| 2ary target of higher scoring condition? | | | Yes |
| Final score | 1455 /2100 | % of max score | 69% |
| Rank: | 0.87 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Primary target, inclusion in uniform panel**

**COMMENT**

There is a wide range of phenotype in Hb S/ß-Thal with those with S/ß° presenting similarly to SS and the ß+ varying considerably by the severity of the mutations. Both individually and as a group, the sickle cell anemias scored in the top 6 - 13 conditions and are clearly important for newborn screening.

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| CONDITION | Variant hemoglobinopathies (including Hb E) |
|---|---|
| TYPE of DISORDER | Hematology, Hemoglobinopathies |
| ETHNICITY | Panethnic for the group; Hb E is most common in parts of southeast Asia; Hb C is most common in those of West African ancestry; Hb D in the Punjab region. |
| SCREENING METHOD(S) | High pressure liquid chromatography (HPLC) and isoelectric focusing (IEF) |
| NBS STATUS in the US | Screened for in 49of 51 states, 99% of annual births (August 2004) |

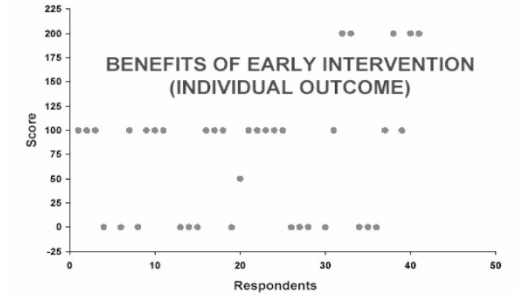
| Responses: | 41 | Valid scores: | 677 | 92% | PubMed references (August 2004) | 510 |
|---|---|---|---|---|---|---|

| Gene | *Many* | Locus | *Many* | OMIM | *Multiple* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | >1:50,000 | 51% | Incidence of the group varies depending on which variants are considered clinically significant. Screening detects a variant that must next be identified. Individual variants are rare, though Hb E is most common [1, 2, 3]. |
| Phenotype at birth | Almost never | 90% | Not apparent at birth. Clinically significant variants cosegregating with ß-thal mutation, it may present in 1st - 2nd year of life depending on severity of individual mutations [1,2]. |
| Burden if untreated | Mild | 40% | Can lead to complications of sickle cell disease when variant is associated with an S allele (e.g., HbS/O-Arab) with hemolysis, vascular occlusion & tissue ischemia leads to injury to every organ or to thalassemia intermedia (e.g., HbE/ß°-thal) with severity related to the ß°-thalassemia mutation [4-6]. |
| The test | | | |
| Screening test | Yes | 85% | Primary screening done by HPLC or IEF in most states to detect unknown variants. Confirmation often requires molecular or mass spectrometry methods on the same specimen [7]. |
| Doable in DBS or by physical method | Yes | 90% | Yes, see [7]. |
| High throughput | No | 71% | Yes, see [7]. |
| Overall cost <$1 | No (>$1/Test) | 55% | Cost per test varies with reporting practices for variant hemoglobinopathies [8]. |
| Multiple analytes | No | 70% | Yes, see [7]. |
| Secondary targets | No | 58% | Yes, see [7]. |
| Multiplex platform | Yes | 39% | Yes, see [7]. |
| The treatment | | | |
| Availability & cost | Limited availability | 75% | Experienced pediatric hematologists are moderately available. Prophylactic medications, health maintenance visits and coordination of care are critical [8-15]. |
| Efficacy of treatment | Potential to prevent MOST negative consequences | 30% | Immunizations prevent some infections. Conjugate pneumococcal vaccine and penicillin prophylaxis prevent 80% of life threatening episodes of strep pneumoniae sepsis [9-13]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome (lack of consensus) (*) | 38% | Benefits depend on which variants are inherited in a compound heterozygous fashion with either HbS or ß- thalassemia mutation. Reduced hospitalizations and episodes of pain for the severely affected [9]. |
| Benefits of early identification | SOME benefits to family and society | 64% | Allows detection in relatives. Genetic counseling is available [8]. |
| Prevention of mortality | No | 42% | Sepsis is much less common in the variant hemoglobinopathies [9,11,12,16]. |
| Confirmation of diagnosis | Widely available | 79% | Confirmation with an alternative method (HPLC, complementary electophoretic methods, and DNA) is done on a separate specimen [9,11]. |
| Acute management | Limited availability | 73% | Care for fever, acute chest syndrome, and splenic sequestration is widely available. Some episodes of pain are managed at home. Hydroxyurea can be used to prevent vasoocclusive pain crises and ACS in children [12,13]. |
| Simplicity of therapy | Periodic involvement of a specialist (lack of consensus) (*) | 42% | Some care provided at home. Preventive therapies relatively simple. Care coordination is more complex [1,14-20]. |

**Variant hemoglobinopathies (including Hb E)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page





**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | HPLC |
| 2ary target of higher scoring condition? | | | Yse |
| Final score | 1199 /2100 | % of max score | 57% |
| Rank: | 0.55 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Secondary target**

**COMMENT**

Over 750 Hb variants have been described. The California Newborn Screening Program considers 27 to be of clinical significance including S/E, S/HPFH/ S/V, S/D, H, alpha-thalassemia major and various combinations of these. Depending on the combinations of these much rarer alleles, phenotypes can range from those seen in sickle cell anemia to very much milder forms. Although disease is milder than in SCA, complications such as proliferative retinopathy and osteonecrosis of the hips, are progressive. Both individually and as a group, the sickle cell anemias scored in the top 6 - 13 conditions and are clearly important for newborn screening. The expert group reaffirmed prior recommendations that all clinically significant results from a newborn screen be reported.

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20. Vichinsky E. New therapies in sickle cell disease. Lancet 2002;360:629-31.

| CONDITION | Glucose-6-phosphate dehydrogenase deficiency |
|---|---|
| TYPE of DISORDER | Hematologic disorder |
| ETHNICITY | Significant variability. |
| SCREENING METHOD(S) | Fluorescent spot assay for G6PD activity |
| NBS STATUS in the US | Screened for in 3 of 51 states, 6% of annual births (August 2004) |

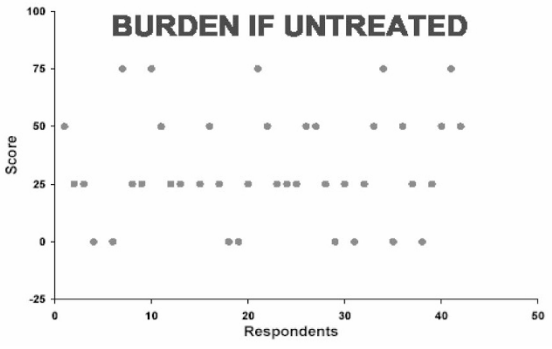
| Responses: | 42 | Valid scores: | 701 | 93% | PubMed references (August 2004): | 11,495 |
|---|---|---|---|---|---|---|

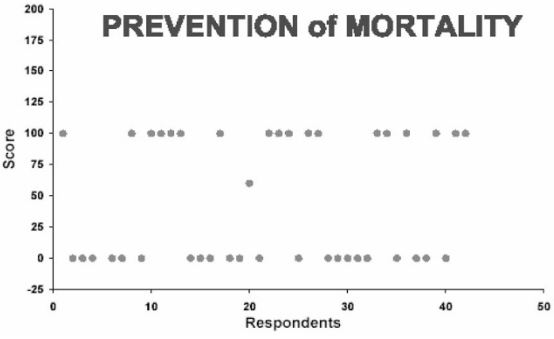
| Gene | *G6PD* | Locus | *Xq28* | OMIM | *305900* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | >1:25,000 | 68% | Gene frequencies of 5% - 25% in tropical Africa, Middle East, Tropical/Subtropical Asia, Mediterranean [1]. |
| Phenotype at birth | Never | 85% | Varies with the severity of the G6PD mutations. Ranges from no signs and symptoms to severe anemia and/or hyperbilirubinemia and jaundice (rarely) [1,2]. |
| Burden if untreated | Moderate (lack of consensus) (*) | 38% | Most are asymptomatic and never express related phenotypes. Induced acute hemolytic anemia and neonatal jaundice occur. G6PD deficiency accounts for as much as 1/3 of kernicterus cases [3-6]. |
| The test | | | |
| Screening test | Yes | 88% | G6PD activity by fluorescent spot test is semi quantitative and may not detect partial deficiencies (e.g., heterozygous females) [1,4,7,8]. Some patients may be identified through bilirubin screening that remains to be fully validated in a general U.S. population setting [6,9,10]. |
| Doable in DBS or by physical method | Yes | 86% | Yes, see [7]. |
| High throughput | Yes | 76% | Yes, see [7]. |
| Overall cost <$1 | <$1/test | 56% | No, stand-alone test [7]. |
| Multiple analytes | No | 8% | No [7]. |
| Secondary targets | No | 11% | No [7]. |
| Multiplex platform | No | 9% | No [7]. |
| The treatment | | | |
| Availability & cost | Widely available | 95% | Severe anemia and/or hyperbilirubinemia may require exchange transfusions or phototherapy. Avoidance of oxidants, antimalarials, sulfonamides, and other red cell stressers [1,2,4-6,11]. |
| Efficacy | Potential to prevent SOME negative consequences | 61% | Identification allows control of exposure to red cell stressers [1,2,6]. Exchange transfusions and/or phototherapy are effective in minimizing progression to kernicterus [5,6,11]. |
| Early intervention | Some evidence that early intervention optimizes outcome | 43% | Identification allows control of exposure to potentially hemolytic agents. [1,2,6]. However, most show little more than episodes of hemolytic anemia [1,2,4]. |
| Early identification | Clear benefits to family and society | 60% | Genetic counseling, prenatal diagnosis [13], and molecular diagnostics [1]. |
| Mortality prevention | No (lack of consensus) (*) | 45% | Rarely, death from a severe hemolytic event occurs [1,11]. |
| Diagn. confirmation | Limited availability | 82% | G6PD activity in hemizygous males and heterozygous females is complicated by X-chromosme inactivation in the female heterozygotes [8]. |
| Acute management | Widely available | 90% | Transfusion therapy for acute hemolytic anemia is widely available as is phototherapy and/or exchange transfusion for hyperbilirubinemia [5,6]. |
| Simplicity of therapy | No specialist involvement | 80% | Avoidance of exposure to hemolytic agents can be managed by oneself or by a primary care provider and, therefore, is widely available [1]. |

**Glucose-6-phosphate dehydrogenase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | Yes | Type | |
| 2ary target of higher scoring condition? | | No | |
| Final score | 1286 /2100 | % of max score | 61% |
| Rank: | 0.69 %ile | | |
| Observed significant discrepancies with literature | | No | |

**ASSESSMENT**

**Not included in uniform panel (test available)**

**COMMENT**

The outcome of children identified in newborn screening programs in the US is unreported. There are questions about the distribution of mutations in the US population that are associated with more severe phenotypes and the risk of exposures to red cell stressors. On the basis of an inadequate understanding of the natural history of those with the mutations characteristic of the US population and the associated risk factors, the condition was not recommended for newborn screening.

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| 10 | Rubaltelli FF et al. Transcutaneous bilirubin measurement: a multicenter evaluation of a new device. Pediatrics 2001;107:1264-71. |
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| 15 | Luisada L. Favism: A singular disease affecting red blood cells. Medicine 1941;20:229. |

# CREATINE METABOLISM DISORDERS

| CONDITION | Guanidinoacetate methyltransferase deficiency |
|---|---|
| TYPE of DISORDER | Inborn error, disorder of creatine metabolism |
| ETHNICITY | No known ethnic variation. |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

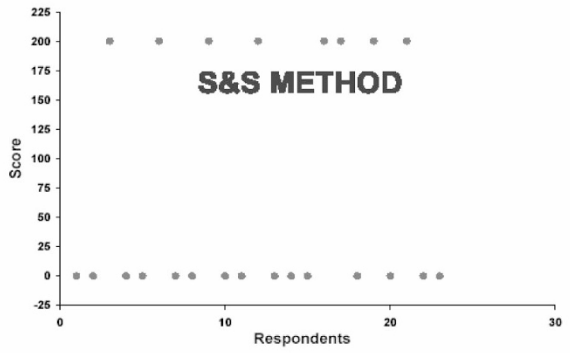
| Responses: | 23 | Valid scores: | 410 | 99% | PubMed references (August 2004) | 38 |
|---|---|---|---|---|---|---|

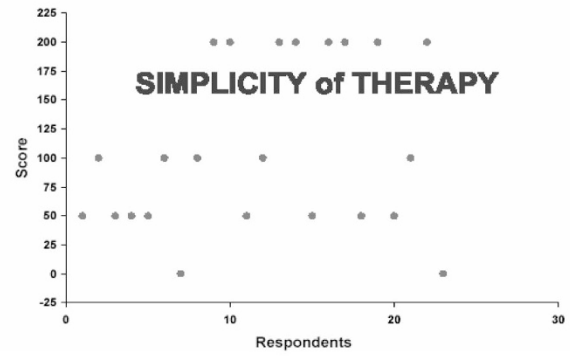
| Gene | *GAMT* | Locus | *19p13.3* | OMIM | *601240* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 5% | Unknown, very few patients described [1]. |
| Phenotype at birth | Almost never | 92% | Presents in first few months of life as developmental delay [2,3,4,5]. |
| Burden if untreated | Severe | 86% | Progressive encephalopathy and mental retardation [2-6]. |
| The test | | | |
| Screening test | No (lack of consensus) (*) | 35% | No test has been validated in a large general population in a public health setting. |
| Doable in DBS or by physical method | No | 30% | No available evidence at the present time. |
| High throughput | No | 30% | No available evidence at the present time. |
| Overall cost <$1 | No (>$1/test) | 22% | No available evidence at the present time. |
| Multiple analytes | No | 18% | No available evidence at the present time. |
| Secondary targets | No | 17% | No available evidence at the present time. |
| Multiplex platform | No | 18% | No available evidence at the present time. |
| The treatment | | | |
| Availability & cost | Widely available | 85% | Creatine supplementation and monitoring requires metabolic specialist [1,5-7]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 34% | Creatine monohydrate supplementation with monitoring of plasma creatine and creatine excretion improves some of the phentotype if started early. Mental retardation persists [2,3,4,6,7]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 48% | Seems to improve motor function but does not fully resolve developmental delay. Not known if limitations are due to late initiation of treatment [1,4,6]. |
| Benefits of early identification | CLEAR benefits to family and society | 76% | Genetic counseling is available. |
| Prevention of mortality | Yes | 28% | Mortality due to intractable seizures can be prevented [8]. |
| Confirmation of diagnosis | Limited availability | 41% | Excess guandinoacetate in body fluids and lack of GAMT activity in cells [2]. |
| Acute management | Limited availability | 57% | Creatine supplementation and monitoring requires a metabolic specialist [1]. |
| Simplicity of therapy | Periodic involvement of specialist (lack of consensus) (*) | 54% | Creatine supplementation and monitoring requires a metabolic specialist [1]. |

**Guanidinoacetate methyltransferase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No test |
| Final score | 922 /2100 | % of max score | 44% |
| Rank: | 0.24 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

GAMT deficiency lacks a validated screening test.

**REFERENCES AND WEB SITES**


| | |
|---|---|
| 1 | von Figura K et al. Guanidinoacetate Methyltransferase Deficiency. In: Scriver, et al., eds. The Metabolic and Molecular Basis of Inherited Disease, 8th ed. McGraw-Hill, New York, 2001;1897-908. |
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| 6 | Verhoeven N et al. Plasma creatinine assessment in creatine deficiency: a diagnostic pitfall. J Inherit Metab Dis 2000;23:835-840. |
| 7 | Schulze A et al. Improving treatment of guanidinoacetate methyltransferase deficiency: reduction of guanidinoacetic acid in body fluids by arginine restriction and ornithine supplementation. Mol Genet Metab 2001;74:413-9. |
| 8 | Ganesan V et al. Guanidinoacetate methyltransferase deficiency: new clinical features. Pediatr Neurol 1997;17:155. |

| CONDITION | Arginine: glycine amidinotransferase deficiency |
|---|---|
| TYPE of DISORDER | Inborn Error, disorder of creatine metabolism |
| ETHNICITY | No ethnic variations known. |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

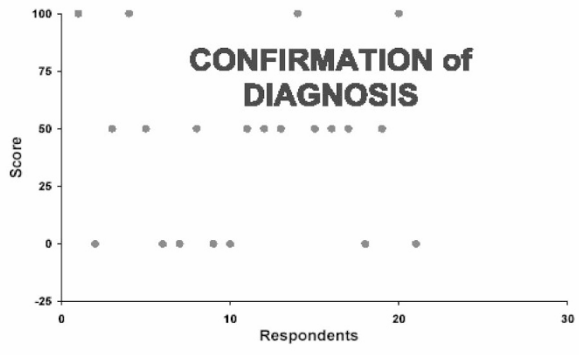
| Responses: | 21 | Valid scores: | 372 | 98% | PubMed references (August 2004) | 39 |
|---|---|---|---|---|---|---|

| Gene | *GATM* | Locus | *15q15.3* | OMIM | *602360* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 1% | Not known; very few patients described [1,2,3,4]. |
| Phenotype at birth | Almost never | 92% | Presents in first few months of life as developmental delay [1,2,3,4]. |
| Burden if untreated | Profound | 85% | Progressive encephalopathy and mental retardation [1,2,3,4]. |
| The test | | | |
| Screening test | No | 33% | No test has been validated in a large general population in a public health setting. Determination of guanidinoacetate in dried blood spots is technically feasible by MS/MS and may be applicable to newborn screening [1,5]. |
| Doable in DBS or by physical method | No | 24% | Not applicable. |
| High throughput | No | 24% | Not applicable. |
| Overall cost <$1 | No (>$1/test) | 14% | Not applicable. |
| Multiple analytes | No | 14% | Not applicable. |
| Secondary targets | No | 14% | Not applicable. |
| Multiplex platform | No | 14% | Not applicable. |
| The treatment | | | |
| Availability & cost | Widely available | 83% | Creatine is available as over-the-counter product [1,5]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 34% | Creatine monohydrate supplementation with monitoring of plasma creatine and creatine excretion improves some of the phenotype if started early. Mental retardation persists [1,2,3,4,5]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 45% | Seems to improve motor function but does not fully resolve developmental delay. Not known if limitations are due to late initiation of treatment [1,4]. |
| Benefits of early identification | CLEAR benefits to family and society | 76% | Genetic counseling is available. |
| Prevention of mortality | No | 25% | Mortality due to intractable seizures can be prevented [1]. |
| Confirmation of diagnosis | Limited availability (lack of consensus) (*) | 43% | Excess guandinoacetate in body fluids and lack of AGAT activity in cells [1,2]. |
| Acute management | Limited availability | 58% | Creatine supplementation and monitoring requires a metabolic specialist [1,2,5]. |
| Simplicity of therapy | Periodic involvement of specialist (lack of consensus) (*) | 45% | Creatine supplementation and monitoring requires a metabolic specialist [1,2,5]. |

**Arginine: glycine amidinotransferase deficiency**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page





**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 861 /2100 | % of max score | 41% |
| Rank: | 0.2 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Fewer than 5 cases of AGAT have been described in the literature. AGAT deficiency lacks a validated screening test

**REFERENCES AND WEB SITES**


| | |
|---|---|
| 1 | von Figura K et al. Guanidinoacetate methyltransferase deficiency. In: Scriver, et al., eds, The Metabolic and Molecular Basis of Inherited Disease, 8th ed. McGraw-Hill, New York, 2001;1897-908. |
| 2 | Stromberger C et al. Clinical characteristics and diagnostic clues in inborn errors of creatine metabolism. J Inherit Metab Dis 2003;26:299-308. |
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| 5 | Verhoeven N et al. Plasma creatinine assessment in creatine deficiency: a diagnostic pitfall. J Inherit Metab Dis 2000;23:835-840. |

| CONDITION | Creatine transporter defect |
|---|---|
| TYPE of DISORDER | Inborn Error, disorder of creatine metabolism |
| ETHNICITY | No evidence of ethnic variability. |
| SCREENING METHOD(S) | No test available at the present time |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

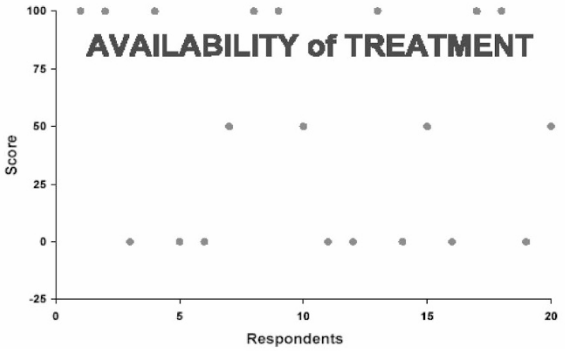
| Responses: | 20 | Valid scores: | 360 | 100% | PubMed references (August 2004) | 1281 |
|---|---|---|---|---|---|---|

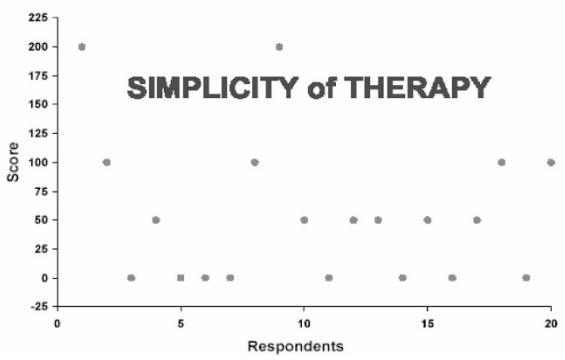
| Gene | *SLC6A8* | Locus | *Xq28* | OMIM | *300036* |
|---|---|---|---|---|---|

| SURVEY SCORES<br>Criteria | Consensus | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| The condition | | | |
| Incidence | <1:100,000 | 1% | Not known; 6/288 (2.1%) cases of nonsyndromal X-linked mental retardation had mutations in SLC6A8 [1]. |
| Phenotype at birth | Almost never | 96% | Midface hypoplasia may be apparent at birth [2-5]. |
| Burden if untreated | Profound | 89% | Severe mental retardation with speech and behavioral abnormalities, autistic behavior, hypotonia, and seizures in males and mild cognitive impairment in females [3,4,5]. |
| The test | | | |
| Screening test | No | 20% | No test has been validated in a large general population in a public health setting. |
| Doable in DBS or by physical method | No | 15% | No available evidence at the present time. |
| High throughput | No | 10% | No available evidence at the present time. |
| Overall cost <$1 | No (>$1/test) | 15% | No available evidence at the present time. |
| Multiple analytes | No | 10% | No available evidence at the present time. |
| Secondary targets | No | 10% | No available evidence at the present time. |
| Multiplex platform | No | 10% | No available evidence at the present time. |
| The treatment | | | |
| Availability & cost | Limited availability (lack of consensus) (*) | 50% | Patients have not been identified prospectively to determine whether creatine supplementation as used in GAMT and AGAT may alter outcome [5,6]. |
| Efficacy of treatment | Treatment efficacy not proven | 16% | Patients have not been identified prospectively to determine whether creatine supplementation as used in GAMT and AGAT may alter outcome [5-7]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 25% | Patients have not been identified prospectively to determine whether creatine supplementation as used in GAMT and AGAT may alter outcome [5,6]. |
| Benefits of early identification | CLEAR benefits to family and society | 75% | Genetic counseling and prenatal diagnosis are feasible [1,3]. |
| Prevention of mortality | No | 20% | Mortality is not significantly reduced. No proven treatment. |
| Confirmation of diagnosis | Only a few centers | 38% | Determination of GAMT and creatine. DNA testing is feasible but there is significant molecular heterogeneity [1-7]. |
| Acute management | Limited availability | 43% | Creatine supplementation and monitoring require a metabolic specialist. Treatment efficacy is higher in females [1-7]. |
| Simplicity of therapy | Regular involvement of specialist (lack of consensus) (*) | 28% | Creatine supplementation and monitoring require a metabolic specialist [1-7]. |

**Creatine transporter defect**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 64 /2100 | % of max score | 31% |
| Rank: | 0.04 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

7 males and 3 females from three families have been reported with this recently described condition. Additional cases from a survey of X-linked mental retardation are not yet described in the literature.

**REFERENCES AND WEB SITES**


| | |
|---|---|
| 1 | Rosenberg EH et al. High prevalence of SLC6A8 deficiency in X-linked mental retardation. Am J Hum Genet 2004;75:97-105. |
| 2 | Salomons GS et al. X-linked creatine-transporter gene (SLC6A8) defect: a new creatine-deficiency syndrome. Am J Hum Genet 2001;68:1497-500. |
| 3 | Hahn KA et al. X-linked mental retardation with seizures and carrier manifestations is caused by a mutation in the creatine-transporter gene (SLC6A8) located in Xq28. Am J Hum Genet 2002;70:1349-1356. |
| 4 | Bizzi A et al. X-linked creatine deficiency syndrome: a novel mutation in creatine transporter gene SLC6A8. Ann Neurol 2002;52:227-231. |
| 5 | Stromberger C et al. Clinical characteristics and diagnostic clues in inborn errors of creatine metabolism. J Inherit Metab Dis 2003;26:299-308. |
| 6 | Item CB, et al. Arginine:glycine amidinotransferase deficiency: the third inborn error of creatine metabolism in humans. Am J Hum Genet 2001;69:1127-1133. |
| 7 | Salomons GS et al. X-linked creatine-transporter gene defect: An overview. J Inherit Metab 2003;26:309-18. |
| 8 | Verhoeven N et al. Plasma creatinine assessment in creatine deficiency: a diagnostic pitfall. J Inherit Metab Dis 2000;23:835-840. |

# LYSOSOMAL STORAGE DISORDERS

| CONDITION | Fabry disease |
|---|---|
| TYPE of DISORDER | Inborn error, lysosomal storage disease |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

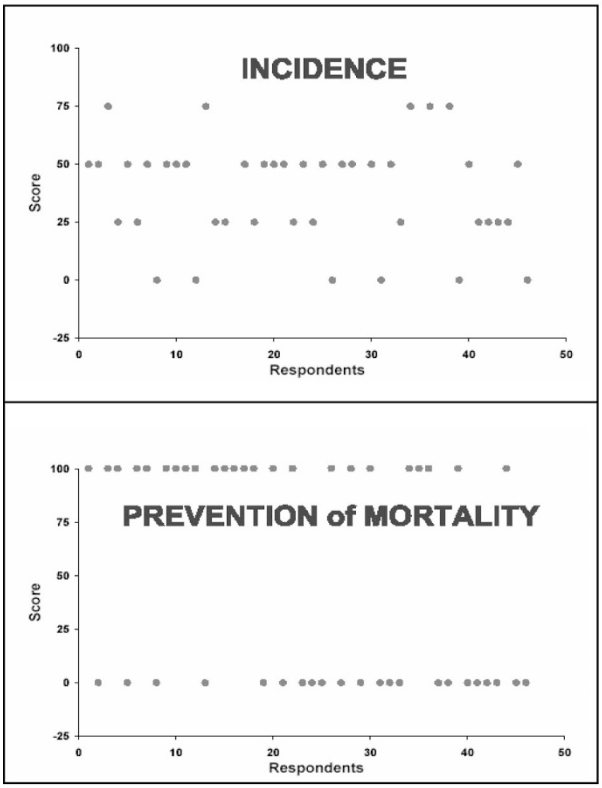
| Responses: | 46 | Valid scores: | 780 | 94% | PubMed references (August 2004) | 2,466 |
|---|---|---|---|---|---|---|

| Gene | *GLA* | Locus | *Xq22* | OMIM | *301500* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 39% | Not known. Estimated at 1:40,000-50,000 males. <1% of female carriers have the classical phenotype [1-3]. |
| Phenotype at birth | Almost never | 99% | Clinical onset usually occurs in childhood or adolescence but may be delayed to the 2nd or 3rd decade [1]. |
| Burden if untreated | Severe | 77% | Initially pain and paresthesias in extremities and vessel ectasia. Renal failure and uremia, cardiac or cerebrovascular disease leading to early death [1]. |
| The test | | | |
| Screening test | No | 22% | No sensitive and specific population-based screening test has been validated. New tests are in clinical trials [4]. |
| Doable in DBS or by physical method | No | 17% | Not applicable. |
| High throughput | No | 15% | Not applicable. |
| Overall cost <$1 | No (>$1/test) | 5% | Not applicable. |
| Multiple analytes | No | 3% | Not applicable. |
| Secondary targets | No | 5% | Not applicable. |
| Multiplex platform | No | 3% | Not applicable. |
| The treatment | | | |
| Availability & cost | Not available | 23% | Care is supportive with focus on pain management. Enzyme replacement therapy is now available at the time of this analysis [1-7]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 37% | Enzyme replacement therapy has been shown to decrease pain, reverse major clinical manifestations and stabilize renal function [1-7]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 26% | Enzyme replacement therapy has been shown to decrease pain, reverse major clinical manifestations and stabilize renal function [3-6]. |
| Benefits of early identification | SOME benefits to family and society | 55% | Genetic counseling, identification of at-risk family members and prenatal diagnosis are available [1-3]. |
| Prevention of mortality | Yes (lack of consensus) (*) | 52% | Ongoing long-term phase 4 surveillance studies of patients treated with enzyme replacement therapy are expected to confirm prevention of mortality. |
| Confirmation of diagnosis | Limited availability | 48% | α-galactosidase A activity in hemizygous males but less sensitive in females [8] who require mutation analysis [9]. |
| Acute management | Only a few centers | 39% | Pain management [3,7], enzyme replacement, renal transplantation are only available in limited centers [1-3]. |
| Simplicity of therapy | Regular involvement of specialist | 13% | Metaboliic physicians and other specialists are required [2,4]. |

**Fabry disease**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 661 /2100 | % of max score | 31% |
| Rank: | 0.05 %ile | | |
| Observed significant discrepancies with literature | | | Yes |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

There is a classic form and a cardiac and renal variant form of Fabry disease, an X-linked condition primarily affecting males. Fabrazyme ® for enzyme replacement therapy was approved by the FDA in 2003, after the primary survey data was collected for this analysis leading to discrepancies between survey data and the literature evidence. Newborn screening tests for Fabry disease are in clinical trials.

**REFERENCES AND WEB SITES**


| | |
|---|---|
| 1 | Desnick RJ et al. α-galactosidase A deficiency: Fabry Disease. In: Scriver CR er al., eds. The Metabolic and Molecular Basis of Inherited Disease, 8th ed. McGraw-Hill, New York, 2001;:3733-74. |
| 2 | Desnick RJ, Astrin K . Fabry disease. (as of 08-05-04) Gene Reviews, http://www.geneclinics.org . |
| 3 | Desnick RJ et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management and enzyme replacement therapy. Ann Intern Med 2003;138:338-46. |
| 4 | Li Y, Chamoles N, et al. Direct multiplex assay of lysosomal enzymes in dried blood spots for newborn screening. Clin Chem 2004;50:1785-96. |
| 5 | Eng CM et al. Safety and efficacy of recombinant human alpha-galactosidase A-replacement therapy in Fabry's disease. N Engl J Med 2001;345:9-16. |
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| 7 | Wilcox WR et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet 2004;75:65-74. |
| 8 | Lockman LA et al. Relief of pain of Fabry's disease by phenylhydantoin. Neurology 1973;23:871. |
| 9 | Mayes JS et al. Differential assay for lysosomal alpha-galactosidases in human tissues and its application to Fabry's disease. Clin Chim Acta 1981;112:247. |
| 10 | Ashton-Prolla P et al. Fabry disease: twenty-two novel mutations in the alpha-galactosidase gene and genotype/phenotype correlations in severely and mildly affected hemizygotes and heterozygotes. J Investig Med 2000;48:227-35. |

| CONDITION | Krabbe disease |
|---|---|
| TYPE of DISORDER | Inborn error, lysosomal storage disease |
| ETHNICITY | Panethnic; higher incidence in Scandinavia. |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

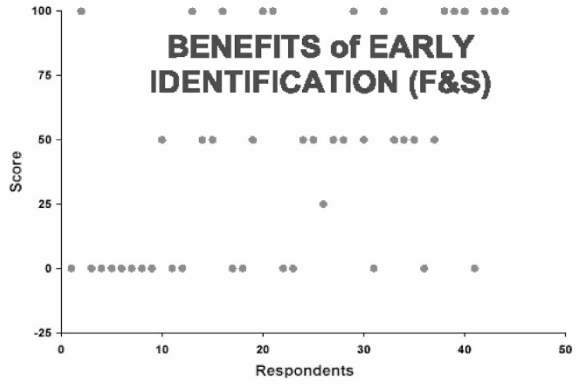
| Responses: | 44 | Valid scores: | 723 | 91% | PubMed references (August 2004) | 604 |
|---|---|---|---|---|---|---|

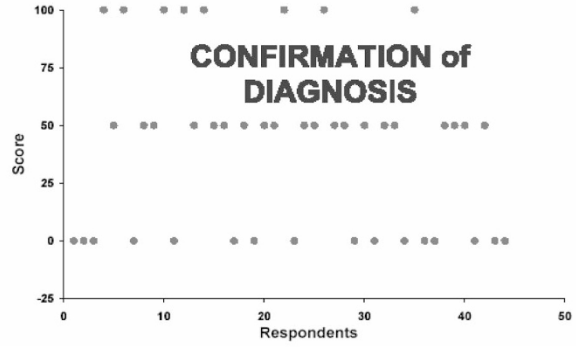
| Gene | *GALC* | Locus | *14q31* | OMIM | *245200* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 14% | 1:100,000 [1]. |
| Phenotype at birth | Almost never | 91% | Infantile form usually presents between 2-3 months and 6 months [1,2,3]. |
| Burden if untreated | Profound | 97% | Developmental delay in first 6 months progressing to hypertonicity, psychomotor regression leading to a decerebrate state and death [2,3]. |
| The test | | | |
| Screening test | No | 11% | No sensitive and specific population-based screening test has been validated. |
| Doable in DBS or by physical method | No | 11% | Not applicable. |
| High throughput | No | 8% | Not applicable. |
| Overall cost <$1 | No (>$1/test) | 6% | Not applicable. |
| Multiple analytes | No | 6% | Not applicable. |
| Secondary targets | No | 3% | Not applicable. |
| Multiplex platform | No | 6% | Not applicable. |
| The treatment | | | |
| Availability & cost | Not available | 6% | Treatment of infantile-onset form is limited to supportive care to control irritability and spasticty [3,4]. |
| Efficacy of treatment | Treatment efficacy not proven | 8% | Treatment of infantile-onset form is limited to supportive care to control irritability and spasticty [3]. Long-term outcome of hematopoietic stem cell transplants is not known [4-6]. |
| Benefits of early intervention | NO evidence that early intervention optimizes individual outcome | 14% | Supportive care to control irritability and spasticty can improve quality of life but has a limited impact on mortality of the severely affected infants. [3]. |
| Benefits of early identification | SOME benefits to family and society (lack of consensus) (*) | 45% | Genetic counseling and prenatal diagnosis are available [3,7,8]. |
| Prevention of mortality | No | 16% | Patients with infantile-onset form rarely live beyond 2 yrs of age [2]. Those with juvenile late-onset form usually die within 2 yrs of onset. [7,8]. |
| Confirmation of diagnosis | Limited availability (lack of consensus) (*) | 41% | Galactocerebrosidase activity assay requires highly specialized laboratory [1]. Molecular testing is available [8]. |
| Acute management | Only a few centers | 26% | Bone marrow transplantation for late-onset and those identified prior to symptomatology is of limited availability [1,2]. |
| Simplicity of therapy | Regular involvement of specialist | 6% | Requires involvement of specialists [1,2,4]. |

**Krabbe disease**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 447 /2100 | % of max score | 21% |
| Rank: | 0 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

The infantile form accounts for 85 - 90% of cases. 10 - 15% are late onset between 6 months and 50 yrs.

**REFERENCES AND WEB SITES**


| | |
|---|---|
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| CONDITION | Hurler, Scheie, Hurler-Scheie disease (MPS I) |
|---|---|
| TYPE of DISORDER | Inborn error, lysosomal storage disorder |
| ETHNICITY | Panethnic. |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

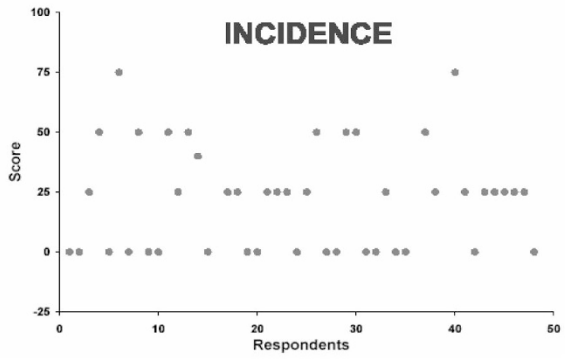
| Responses: | 48 | Valid scores: | 801 | 93% | PubMed references (August 2004) | 380 |
|---|---|---|---|---|---|---|

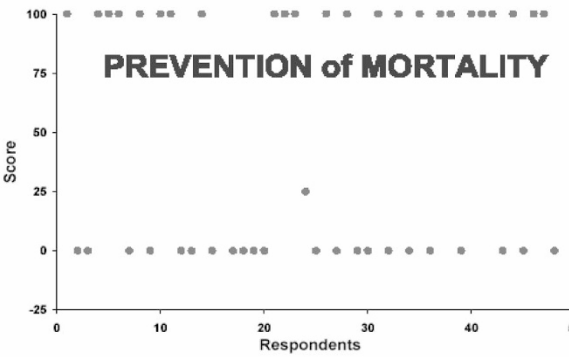
| Gene | *IDUA* | Locus | *4p16.3* | OMIM | *252800* |
|---|---|---|---|---|---|

| SURVEY SCORES | | | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | % of max score | |
| The condition | | | |
| Incidence | >1:75,000 (lack of consensus) (*) | 22% | 1:100,000 severe form; 1:500,000 mild form (see comments) [1,2]. |
| Phenotype at birth | Almost never | 90% | Normal at birth; coarsening facial features over first two years in severe form [3]. |
| Burden if untreated | Profound | 86% | Progression to profound mental retardation and death from cardiorespiratory failure in first 10 years in severe form [4]. |
| The test | | | |
| Screening test | No | 31% | No sensitive and specific population-based screening test has been validated. |
| Doable in DBS or by physical method | No | 21% | Not applicable. |
| High throughput | No | 18% | Not applicable. |
| Overall cost <$1 | No (>$1/test) | 11% | Not applicable. |
| Multiple analytes | No | 13% | Not applicable. |
| Secondary targets | No | 10% | Not applicable. |
| Multiplex platform | No | 13% | Not applicable. |
| The treatment | | | |
| Availability & cost | Not available | 14% | Supportive therapies, bone marrow transplants (BMT) and enzyme replacement therapies are of limited availability and are costly [4-11]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences | 31% | Supportive therapies can improve quality of life [4,5]. Bone marrow transplant outcomes are variable but may slow progression and improve survival in some [4,5,9-11]. There is evidence that ERT reverses some features but not all, though not yet shown in presymptomatic cases [6-8]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome | 42% | Supportive therapies can improve quality of life [4,5]. Bone marrow transplant outcomes are variable but may slow progression and improve survival in some [9-11]. |
| Benefits of early identification | SOME benefits to family and society | 63% | Genetic counseling, molecular testing and prenatal diagnosis are available [3,12,13,15]. |
| Prevention of mortality | Yes (lack of consensus) (*) | 52% | BMT and ERT reverse some aspects of the phenotypes and extend life [3,4,5,9-11]. |
| Confirmation of diagnosis | Limited availability | 48% | Assay of α-L-iduronidase [12,14,16] and DNA mutation testing are available [13]. |
| Acute management | Limited availability | 30% | Metabolic physicians and other specialists may be of limited availability [3]. |
| Simplicity of therapy | Regular involvement of specialist | 11% | Metabolic physicians and other specialists are involved in complex care [3]. |

**Hurler, Scheie, Hurler-Scheie disease (MPS I)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 707 /2100 | % of max score | 34% |
| Rank: | 0.07 %ile | | |
| Observed significant discrepancies with literature | | | No |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

MPS-I includes Hurler, Hurler-Scheie and Scheie syndromes. However, there are no clear clinical criteria that discriminate between them. Hurler patients represent the severe form, Hurler-Scheie tends to be an intermediate form and Scheie a mild form but are less easily distinguished from each other than from 'Hurler'. Aldurazyme ® was recently approved by FDA based on its benefit to those already symptomatic. Little information is available as to efficacy in presymtomatic cases.

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| | |
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| CONDITION | Pompe disease (glycogen storage disease type II) |
|---|---|
| TYPE of DISORDER | Inborn error, lysosomal storage disease |
| ETHNICITY | 1:50,000 Chinese; 1:40,000 Dutch. |
| SCREENING METHOD(S) | No test |
| NBS STATUS in the US | Screened for in 0 of 51 states, 0% of annual births (August 2004) |

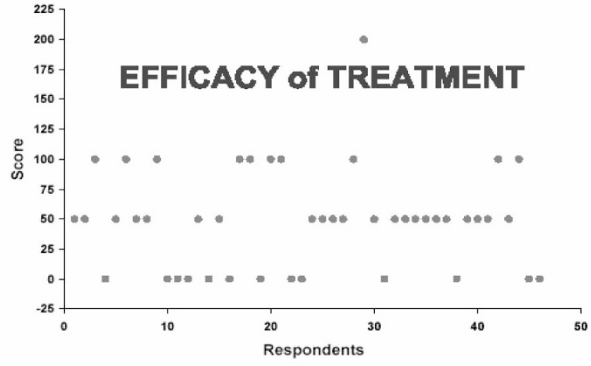
| Responses: | 46 | Valid scores: | 772 | 93% | PubMed references (August 2004) | 572 |
|---|---|---|---|---|---|---|

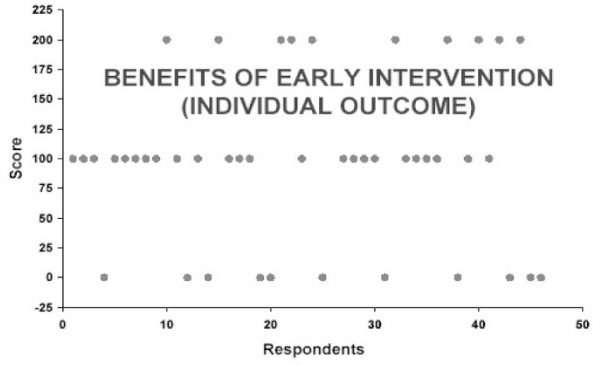
| Gene | *AMD* | Locus | *17q25.2-q25.3* | OMIM | *232300* |
|---|---|---|---|---|---|

| SURVEY SCORES | | % of max score | LITERATURE AND WEB-BASED EVIDENCE [References] |
|---|---|---|---|
| **Criteria** | **Consensus** | | |
| The condition | | | |
| Incidence | <1:100,000 | 20% | 1:300,000 [1-4]; 1:68,038 worldwide [5]. |
| Phenotype at birth | <25% of cases | 77% | Most with infantile form present in first few months of life [3,6-8]. |
| Burden if untreated | Profound | 15% | Cardiomegaly and hypotonia. Death from cardiorespiratory failure usually before 1-2 yrs. of age in infantile onset form [3,6-8]. |
| The test | | | |
| Screening test | No | 15% | No sensitive and specific screening test that is validated in a general population is available at the current time. |
| Doable in DBS or by physical method | No | 12% | A multiplex assay on dried blood spots has been reported [16]. |
| High throughput | No | 15% | Not applicable. |
| Overall cost <$1 | No (>$1/test) | 5% | Not applicable. |
| Multiple analytes | No | 3% | Not applicable. |
| Secondary targets | No | 3% | Not applicable. |
| Multiplex platform | No | 11% | Multiplex testing on dried blood spots is reported [16]. |
| The treatment | | | |
| Availability & cost | Not available | 5% | Supportive therapy can slow disease progression. Dietary management may improve some functions. Enzyme replacement therapy (ERT) is in clinical trials in the US [3,6,9-11, 17,18]. |
| Efficacy of treatment | Potential to prevent SOME negative consequences (*) | 25% | About 25% with adult-onset form on high protein diet may show improved respiratory or skeletal muscle function[3,6,9,10]. ERT has been shown to extend life and improve skeletal muscle function [12,17,18]. |
| Benefits of early intervention | SOME evidence that early intervention optimizes individual outcome (*) | 49% | Dietary treatment improves respiratory function [11]. ERT results are encouraging [17,18]. |
| Benefits of early identification | SOME benefits to family and society | 62% | Genetic counseling and prenatal diagnosis available [3,6,13,14,17,18]. |
| Prevention of mortality | Yes | 57% | Mortality rates may be reduced in adult onset form; not in infantile form (see comments) [6,9]. ERT results are encouraging [17,18]. |
| Confirmation of diagnosis | Only a few centers | 39% | α-glucosidase activity in fibroblasts or muscle and measurement of oligosacchairdes by MS/MS are not widely available assays [3,10-12,15]. |
| Acute management | Only a few centers | 21% | Dietary and ventilatory support. Clinical trials of therapeutics are available in limited centers [3,6,9,10,12,18]. |
| Simplicity of therapy | Regular involvement of specialist | 6% | Regular involvement of specialists is required [3,6]. |

**Pompe disease (glycogen storage disease type II)**

**CRITERIA OF LEAST CONSENSUS** see (*) on first page




**INCLUSION CRITERIA**

| | | | |
|---|---|---|---|
| Test available | No | Type | No test |
| 2ary target of higher scoring condition? | | | No |
| Final score | 613 /2100 | % of max score | 29% |
| Rank: | 0.01 %ile | | |
| Observed significant discrepancies with literature | | | |

**ASSESSMENT**

**Not included in uniform panel (no test)**

**COMMENT**

Although no definitive treatment was available at the time of this report, enzyme replacement therapy is in clinical trials and led many of those involved in those trials to respond that a treatment was "available" [14]. Early ERT results are encouraging. *Authors' note: Myozyme ® (alglucosidase alfa) was approved by the FDA for treatment of Pompe Disease in April 2006.*

**REFERENCES AND WEB SITES**


| | |
|---|---|
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**Appendix 2**

# HRSA/ACMG UNIFORM CONDITION PANEL EVALUATION TOOL

## INSTRUCTIONS

This tool is to aid NBS Advisory Committee of individual States/Regions (or ad hoc expert panels) involved in the assessment of the NBS "fitness" of conditions currently not screened for in their program but included in the HRSA/ACMG uniform condition panel

| | | | |
|---|---|---|---|
| NAME | | Phone | |
| INSTITUTION | | Fax | |
| DATE | | E-mail | |

| | |
|---|---|
| ADDRESS | |

| CHECK ALL CATEGORIES THAT APPLY TO YOU | | | |
|---|---|---|---|
| ☐ | Provider of Screening Services (TESTING) | ☐ | Provider of Diagnostic Services |
| ☐ | Provider of Screening Services (FOLLOW UP) | ☐ | Primary Care Provider |
| ☐ | Provider of Screening Services (ADMINISTRATION) | ☐ | Specialty Care Provider |
| ☐ | Provider of Screening Services (POLICY) | ☐ | Consumer |

**The evaluation tool includes:**

1. This page of INSTRUCTIONS
2. A page listing CRITERIA and SCORES
3. A worksheet listing NBS REFERENCE CONDITIONS. Scoring these well known conditions is encouraged to self-assess how the respondent's scores compare with the results of the HRSA/ACMG survey (listed at the top)
4. A blank worksheets where to list the condition(s) under evaluation for inclusion/esclusion

**To better define a condition under evaluation, consider including the name of the deficient enzyme and the OMIM number together with the common name of the disorder**

**For each criterion, enter one of the scores provided. If unsure, enter "U"**
**A BLANK means ZERO**

**After completing the tool, please mail or fax it to your project coordinator (see below)**

**Thank you for your participation**

**PROJECT COORDINATOR**

| | |
|---|---|
| NAME | |
| ADDRESS | |

| | | | |
|---|---|---|---|
| PHONE | | FAX | |
| E-MAIL | | | |

| CRITERIA | CATEGORIES | SCORE |
|---|---|---|
| **Incidence of condition** | >1:5,000 | 100 |
| | >1:25,000 | 75 |
| | >1:50,000 | 50 |
| | >1:75,000 | 25 |
| | <1:100,000 | 0 |
| **Sign & Symptoms clinically identifiable in the first 48 hours** | Never | 100 |
| | <25% of cases | 75 |
| | <50% of cases | 50 |
| | <75% of cases | 25 |
| | Always | 0 |
| **Burden of disease**<br><br>**(Natural Hx if untreated)** | Profound | 100 |
| | Severe | 75 |
| | Moderate | 50 |
| | Mild | 25 |
| | Minimal | 0 |
| **Does a sensitive AND specific screening test currently exist?** | YES | 200 |
| | NO | 0 |
| **Test characteristics (Yes = apply score; No = zero)** | Doable in neonatal blood spots **OR** by a simple, in-nursery physical method | 100 |
| | High throughput (>200/day/FTE) | 50 |
| | Overall analytical cost <1$ per test per condition | 50 |
| | Multiple analytes relevant to one condition are detected in same run | 50 |
| | Other conditions identified by same analytes | 50 |
| | Multiple conditions detected by same test (multiplex platform) | 200 |
| **Availability of treatment** | Treatment exists and is widely available in most communities | 50 |
| | Treatment exists but availability is limited | 25 |
| | No treatment available or necessary | 0 |
| **Cost of treatment** | Inexpensive | 50 |
| | Expensive (>$50,000/patient/year) | 0 |
| **Potential efficacy of existing treatment** | To prevent ALL negative consequences | 200 |
| | To prevent MOST negative consequences | 100 |
| | To prevent SOME negative consequences | 50 |
| | Treatment efficacy not proven | 0 |
| **Benefits of early intervention (INDIVIDUAL OUTCOME)** | Clear scientific evidence that early intervention resulting from screening optimizes outcome | 200 |
| | Some scientific evidence that early intervention resulting from screening optimizes outcome | 100 |
| | No scientific evidence that early intervention resulting from screening optimizes outcome | 0 |
| **Benefits of early identification (FAMILY & SOCIETY)** | Early identification provides clear benefits to family and society (education, understanding prevalence and natural history, cost effectiveness) | 100 |
| | Early identification provides some benefits to family and society | 50 |
| | No evidence of benefits | 0 |
| **Early diagnosis and treatment prevent mortality** | YES | 100 |
| | NO | 0 |
| **Availability of diagnostic confirmation** | Providers of diagnostic confirmation are widely available | 100 |
| | Limited availability of providers of diagnostic confirmation | 50 |
| | Diagnostic confirmation is available only in a few centers | 0 |
| **Acute management** | Providers of acute management are widely available | 100 |
| | Limited availability of providers of acute management | 50 |
| | Acute management is available only in a few centers | 0 |
| **Simplicity of therapy** | Management at the primary care or family level | 200 |
| | Requires periodic involvement of a specialist | 100 |
| | Requires regular involvement of a specialist | 0 |
| | Max score | 2100 |

# NEWBORN SCREENING CONDITION EVALUATION TOOL

## Reference Conditions

| | | Deficient ENZYME | Medium chain acyl-CoA dehydrogenase | various | Phenylalanine hydroxylase | Hemoglobin S | 21-hydroxylase |
|---|---|---|---|---|---|---|---|
| | | HRSA/ACMG SURVEY SCORE | 1799 | 1718 | 1663 | 1542 | 1533 |
| | | YOUR SCORE | | | | | |
| | | Common NAME | MCAD deficiency (MCAD) | Congenital Hypothyroidism | Phenyl ketonuria (PKU) | Sickle cell anemia (SCA) | Congenital Adrenal Hyperplasia (CAH) |
| Incidence of condition | >1:5,000 | 100 | | | | | |
| | >1:25,000 | 75 | | | | | |
| | >1:50,000 | 50 | | | | | |
| | >1:75,000 | 25 | | | | | |
| | <1:100,000 | 0 | | | | | |
| Signs & Symptoms clinically identifiable in the first 48 hours | Never | 100 | | | | | |
| | <25% of cases | 75 | | | | | |
| | <50% of cases | 50 | | | | | |
| | <75% of cases | 25 | | | | | |
| | Always | 0 | | | | | |
| Burden of disease if untreated (Natural history if untreated) | Profound | 100 | | | | | |
| | Severe | 75 | | | | | |
| | Moderate | 50 | | | | | |
| | Mild | 25 | | | | | |
| | Minimal | 0 | | | | | |
| Does a sensitive AND specific screening test currently exist? | YES | 200 | | | | | |
| | NO | 0 | | | | | |
| Test characteristics (Yes = apply score No = zero) | Doable in neonatal blood spots OR by a simple, in-nursery physical method | 100 | | | | | |
| | High throughput (>200/day/FTE) | 50 | | | | | |
| | Overall analytical cost <1$ per test per condition | 50 | | | | | |
| | Multiple analytes relevant to one condition are detected in same run | 50 | | | | | |
| | Other conditions identified by same analytes | 50 | | | | | |
| | Multiple conditions detected by same test (multiplex platform) | 200 | | | | | |
| Availability of treatment | Treatment exists and is widely available in most communities | 50 | | | | | |
| | Treatment exists but availability is limited | 25 | | | | | |
| | No treatment available or necessary | 0 | | | | | |
| Cost of treatment | Inexpensive | 50 | | | | | |
| | (Expensive (>$50,000/patient/year) | 0 | | | | | |
| Potential efficacy of existing treatment | To prevent ALL negative consequences | 200 | | | | | |
| | To prevent MOST negative consequences | 100 | | | | | |
| | To prevent SOME negative consequences | 50 | | | | | |
| | Treatment efficacy not proven | 0 | | | | | |
| Benefits of early intervention (INDIVIDUAL OUTCOME) | Clear scientific evidence that intervention resulting from screening optimize outcome | 200 | | | | | |
| | Some scientific evidence that early intervention resulting from screening optimizes outcome | 100 | | | | | |
| | No scientific evidence that early intervention resulting from screening optimizes outcome | 0 | | | | | |
| Benefits of early identification (FAMILY & SOCIETY) | Early identification maximizes benefits (education, understanding prevalence and natural history, cost effectiveness) | 100 | | | | | |
| | Early intervention improves benefits | 50 | | | | | |
| | No evidence of benefits | 0 | | | | | |
| Early diagnosis and treatment prevent mortality | YES | 100 | | | | | |
| | NO | 0 | | | | | |
| Diagnostic confirmation | Providers of diagnostic confirmation are widely available | 100 | | | | | |
| | Limited availability of providers of diagnostic confirmation | 50 | | | | | |
| | Diagnostic confirmation is available only in a few centers | 0 | | | | | |
| Clinical management | Providers of acute management are widely available | 100 | | | | | |
| | Limited availability of providers of acute management | 50 | | | | | |
| | Acute management is available only in a few centers | 0 | | | | | |
| Simplicity of therapy | Management at the primary care or family level | 200 | | | | | |
| | Requires periodic involvement of a specialist | 100 | | | | | |
| | Requires regular involvement of a specialist | 0 | | | | | |

| NEWBORN SCREENING CONDITION EVALUATION TOOL | | Deficient ENZYME | | | | |
|---|---|---|---|---|---|---|
| | | HRSA/ACMG SURVEY SCORE | | | | |
| | | YOUR SCORE | | | | |
| Conditions to be evaluated | | Common NAME | | | | |
| Incidence of condition | >1:5,000 | 100 | | | | |
| | >1:25,000 | 75 | | | | |
| | >1:50,000 | 50 | | | | |
| | >1:75,000 | 25 | | | | |
| | <1:100,000 | 0 | | | | |
| Signs & Symptoms clinically identifiable in the first 48 hours | Never | 100 | | | | |
| | <25% of cases | 75 | | | | |
| | <50% of cases | 50 | | | | |
| | <75% of cases | 25 | | | | |
| | Always | 0 | | | | |
| Burden of disease if untreated (Natural history if untreated) | Profound | 100 | | | | |
| | Severe | 75 | | | | |
| | Moderate | 50 | | | | |
| | Mild | 25 | | | | |
| | Minimal | 0 | | | | |
| Does a sensitive AND specific screening test currently exist? | YES | 200 | | | | |
| | NO | 0 | | | | |
| Test characteristics (Yes = apply score No = zero) | Doable in neonatal blood spots OR by a simple, in-nursery physical method | 100 | | | | |
| | High throughput (>200/day/FTE) | 50 | | | | |
| | Overall analytical cost <1$ per test per condition | 50 | | | | |
| | Multiple analytes relevant to one condition are detected in same run | 50 | | | | |
| | Other conditions identified by same analytes | 50 | | | | |
| | Multiple conditions detected by same test (multiplex platform) | 200 | | | | |
| Availability of treatment | Treatment exists and is widely available in most communities | 50 | | | | |
| | Treatment exists but availability is limited | 25 | | | | |
| | No treatment available or necessary | 0 | | | | |
| Cost of treatment | Inexpensive | 50 | | | | |
| | (Expensive (>$50,000/patient/year) | 0 | | | | |
| Potential efficacy of existing treatment | To prevent ALL negative consequences | 200 | | | | |
| | To prevent MOST negative consequences | 100 | | | | |
| | To prevent SOME negative consequences | 50 | | | | |
| | Treatment efficacy not proven | 0 | | | | |
| Benefits of early intervention (INDIVIDUAL OUTCOME) | Clear scientific evidence that intervention resulting from screening optimize outcome | 200 | | | | |
| | Some scientific evidence that early intervention resulting from screening optimizes outcome | 100 | | | | |
| | No scientific evidence that early intervention resulting from screening optimizes outcome | 0 | | | | |
| Benefits of early identification (FAMILY & SOCIETY) | Early identification maximizes benefits (education, understanding prevalence and natural history, cost effectiveness) | 100 | | | | |
| | Early intervention improves benefits | 50 | | | | |
| | No evidence of benefits | 0 | | | | |
| Early diagnosis and treatment prevent mortality | YES | 100 | | | | |
| | NO | 0 | | | | |
| Diagnostic confirmation | Providers of diagnostic confirmation are widely available | 100 | | | | |
| | Limited availability of providers of diagnostic confirmation | 50 | | | | |
| | Diagnostic confirmation is available only in a few centers | 0 | | | | |
| Clinical management | Providers of acute management are widely available | 100 | | | | |
| | Limited availability of providers of acute management | 50 | | | | |
| | Acute management is available only in a few centers | 0 | | | | |
| Simplicity of therapy | Management at the primary care or family level | 200 | | | | |
| | Requires periodic involvement of a specialist | 100 | | | | |
| | Requires regular involvement of a specialist | 0 | | | | |

**Appendix 3**

**Condition ACT(ion) Sheets**

**Phenylketonuria (PKU)**
**Disease Category**

*Amino Acid Disorder*

**You Should Take The Following Actions:**

- ***Immediate*** **consultation with a metabolic specialist (see below*).**
- **Contact family to inform them of the newborn screening result and arrange a visit for an immediate physical exam of the newborn.**
- **Undertake definitive investigations in consultation with metabolic specialist and referral as indicated.**
- **Report findings to State newborn screening program.**

**Meaning of Screening Result**

**Elevated level of phenylalanine**, especially with **reduced level of tyrosine** and **increased phenylalanine:tyrosine ratio** suggests PKU. Elevated phenylalanine can be associated with disorders other than PKU.

**Condition Description**

PKU is an autosomal recessive genetic condition caused by a defect in phenylalanine hydroxylase (PAH) enzyme defect that impairs the breakdown of an amino acid, phenylalanine, into its product, tyrosine.

**Confirmation Of Diagnosis**

Specific diagnosis is made by confirmatory tests plasma amino acid analysis that shows **increased phenylalanine** and **decreased tyrosine**. It should take no more than one to two days to confirm or exclude the diagnosis.

**Clinical Expectations**

Asymptomatic in the neonate. If untreated PKU will produce irreversible mental retardation, hyperactivity, autism, and seizures.

**Resources for Referral**

*Insert local, state, and regional resource.*

**Additional Information**

**New England Metabolic Consortium—Emergency Protocols**
*http://www.childrenshospital.org/newenglandconsortium/*
**Gene Tests/Gene Clinics** *http://www.genetests.org*
U.S. National Newborn & Genetics Resource Center
*http://www.genes-r-us.uthscsa.edu*

**Newborn Screening Act Sheet**

**[C8]**

**Medium Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency**
**Disease Category**

Fatty acid oxidation disorder (FAOD)

**You Should Take The Following Actions:**

- ***Immediate*** **consultation with a metabolic specialist (see below*).**
- **Contact family to inform them of the newborn screening result, provide feeding instructions (feeding every 2-4 hours.) and schedule an immediate visit. If infant is lethargic or not feeding well, emergency care is warranted.**
- **Emergency treatment includes avoiding fasting, determining blood glucose level and providing glucose if hypoglycemic or symptomatic.**
- **Undertake definitive investigations in consultation with metabolic specialist.**
- **Report findings to State newborn screening program.**

**Meaning Of Screening Result**

**Highly elevated** C8 acylcarnitine (INSERT STATE SPECIFIC CONCENTRATION) likely indicates MCADD. **Milder elevations** of C8 acylcarnitine (INSERT STATE SPECIFIC CONCENTRATION) may indicate MCADD, an MCADD variant, another condition, or transient (false-positive).

**Metabolic Description**

FAOD disorders impair ketogenesis and energy homeostasis. MCAD is due to a defect of the mitochondrial enzyme medium chain acyl-CoA dehydrogenase which is responsible for a middle step in fatty acid oxidation. Hallmark features can include critical hypoketotic hypoglycemia, especially during times of fasting, catabolism, or illness.

**Confirmation of Diagnosis**

Confirmatory biochemical testing includes plasma acylcarnitine and urine acylglycine profiles. Informative markers are **C6-C10 acylcarnitines** in plasma, **hexanoylglycine and suberylglycine** in urine. Both parents, and if applicable, all siblings (of any age) should also be tested. Biochemically affected cases are confirmed by DNA testing.

**Clinical Expectations**

MCADD has variable presentation. The newborn may be asymptomatic. However, the neonate may also have a clinical phenotype that includes hypoglycemia causing lethargy, vomiting and the risk of sudden death.

**Resources for Referral**

*Insert local, state, and regional resources*

**Additional Information**

**New England Metabolic Consortium—Newborn Screening Protocols**
*http://www.childrenshospital.org/newenglandconsortium/*
**Gene Tests/Gene Clinics:** *http://www.genetests.org*
**U.S. National Newborn & Genetics Resource Center**
*http://www.genes-r-us.uthscsa.edu*

**Newborn Screening Act Sheet**

**[Hearing Test]**

**Congenital Hearing Loss**

**Disease Category**

Hearing Loss

**You Should Take The Following Actions:**

- **Contact family and primary care physician to inform them of the newborn hearing screening result.**
- **Repeat the hearing test.**
- **If hearing loss is confirmed, comprehensive genetic evaluation is indicated.**

**Meaning Of Screening Result**

Only 1-3 of 100 infants who screen positive have confirmed hearing loss. However, hearing loss is serious so all infants who screen positive need to be further tested.

**Condition Description**

Defined as hearing loss that is permanent, bilateral or unilateral, sensor or conductive, and averaging loss of 30 decibels or more in the frequency range important for speech recognition. Etiologies are numerous. About 50% are due to environmental factors including ototoxicity of drugs (genetically determined), acoustic trauma, and bacterial or viral infections (e.g., rubella, CMV). The remaining 50% are associated with genetic syndromes.

**Confirmation Of Diagnosis**

Hearing loss is confirmed followed by etiologic diagnosis.

**Disease Expectations**

Even modest levels of bilateral hearing loss can lead to important problems in speech recognition and speech development. Hearing loss can also indicate a genetic syndrome.

**Resources for Referral**

Local, state, regional and national

**Additional Information**

**Gene Tests/Gene Clinics** *www.genetests.org*

**National Center for Hearing Assessment and Management**

*www.infanthearing.org*

**Newborn Screening Act Sheet**

**[Citrulline]**

**Citrullinemia or Argininosuccinic Acidemia**

**Disease Category**

Urea cycle defect (UCD)

**You Should Take The Following Actions:**

- ***Immediate* consultation with a metabolic specialist (see below*)**
- **Contact family to inform them of the newborn screening result, provide feeding instructions (need for dietary restriction of protein) and schedule an immediate visit**
- **Emergency treatment if symptomatic. Evaluate for hyperammonemia.**
- **Undertake definitive investigations in consultation with metabolic specialist.**
- **Report findings to State newborn screening program.**

**Meaning of Screening Result**

**Elevated level of citrulline** suggests either citrullinemia or argininosuccinic acidemia.

**Condition Description**

Urea Cycle Disorders are caused by a defective enzyme resulting in impairment in the ability of the urea cycle to convert one of the breakdown products of protein, ammonia, to the nontoxic product urea. The resulting accumulation of ammonia causes the toxicity of the UCD defects. **Citrullinemia** is caused by a deficiency of argininosuccinic acid synthetase. **Argininosuccinic acidemia** is caused be a deficiency of argininosuccinic acid lyase.

**Confirmation Of Diagnosis**

Takes one to three days to sort out initial follow-up tests including repeat newborn screening; however, critical laboratories such as ammonia should be obtained in the interim. A specific diagnosis can be made by confirmatory tests such as plasma amino acids, urine organic acids, and a urine orotic acid. In **citrullinemia** these tests show **increased plasma and urine citrulline** and **increased urine orotic acid.** In **argininosuccinic acidemia,** the tests will show the **presence of argininosuccinic acid** in urine and plasma (usually more prominent in urine than in plasma) and **increased orotic acid** in urine.

**Clinical Expectations**

Citrullinemia and argininosuccinic acidemia can present in the newborn period with hyperammonemia, failure to thrive, lethargy, and coma. Later signs include mental retardation. In argininosuccinic acidemia, liver disease may also be present.

**Resources for Referral**

*Insert local, state, and regional resources*

**Additional Information**

**New England Metabolic Consortium – Emergency Protocols**

*http://www.childrenshospital.orrg/newenglandconsortium/*

**Gene Tests/Gene Clinics** *http://www.genetests.org*

**U.S. National Newborn Screening & Genetics Resource Center**
*http://www.genes-r-us@uthscsa.edu*

### Newborn Screening Act Sheet

**[TSH,T4]**

**Congenital Hypothyroidism (CH)**

### Disease Category

Endocrinopathy

### You Should Take the Following Actions:

- **Contact family to inform them of the newborn screening result.**
- **Schedule office visit for the newborn within 1 -3 days for repeat screening and/or confirmatory testing.**
- **Consult pediatric endocrinologist; referral to endocrinologist if considered appropriate.**
- **Report findings back to State newborn screening program.**

### Meaning of Screening Result

**Decreased thyroxine (T4)** accompanied by **increased thyroid stimulating hormone (TSH)** suggests primary hypothyroidism; **decreased T4** and **decreased TSH** suggests secondary hypothyroidism.

Some programs screen only for primary hypothyroidism by only measuring TSH. An **increase in TSH** suggests congenital hypothyroidism.

### Metabolic Description

Lack of adequate thyroid hormone production.

### Confirmation Of Diagnosis

Takes 1-3 days. Diagnostic tests include **reduced serum T4, T3 uptake, free T4 or T4 index**, and **serum TSH**, which will be increased in primary hypothyroidism and reduced in secondary hypothyroidism.

### Clinical Expectations

Asymptomatic in the neonate. If untreated, results in developmental delay/mental retardation and poor growth.

### Resources for Referral

*Insert local, state and regional resources*

### Additional Information

**Gene Tests/Gene Clinics** *www.genetests.org*

### Appendix 4

**Program standards**

**Initial Newborn Screening Activities**

1. Document complete reporting of all results of all liveborn newborns within three months of the close of the year (target 100%).
   a. Initial screening specimens should be collected after 24 hours, but as close to discharge as possible. Newborns with prolonged hospital stays should be tested before day seven, regardless of reason for hospitalization.
   b. The number of newborns discharged from hospitals without screening and the number of these infants involved in follow-up testing should be documented.
   c. The number of newborns discharged without screening for which screening occurred through follow-up at some later time should be documented.
2. Document and report the number of out-of-hospital births (e.g., using birth certificates) and the numbers of those tested versus those not tested.
3. Document the number of unsatisfactory specimens for any reason (target is 0%). This includes specimens considered unsatisfactory due to:
   a. laboratory/analytical issues (e.g., a poor specimen);
   b. clinical issues (e.g., timing of specimen acquisition); and
   c. information issues (i.e., inadequate demographics such as name, data completeness such as no discharge time or specimen collection times noted)
4. Document rate of unsatisfactory specimens followed up with a satisfactory test (target 100%)
   a. document the number of newborns discharged prior to 24 hours and retest all;
   b. document the number of newborns discharged prior to 24 hours and initiate a retest of all within 6 days of life; and
   c. monitor unsatisfactory specimen data and report plans for corrective action.
5. Document the number of newborns screened positive or not normal for each disorder on the screening panel. For programs that universally require a second screen, document the number of newborns receiving the required second screen.
6. Document the rates and types of disorders with a confirmed clinical diagnosis.
7. Document time from birth to reporting of all presumptive positive screens.
8. Document time from birth to:
   a. testing to establish diagnosis; and
   b. initiation of intervention or treatment by condition.
9. Document:
   a. that confirmed positives are treated where indicated and comply with the therapeutic program;
   b. appropriate outcome variables, long-term health status, and development, at least annually; and
   c. the offering of services and utilization for positive cases (consider matched controls).

10. Document costs per individual screened, cost of detection of each disorder, and estimated cost avoidance. Ensure that the impact on families is considered.
11. Document (costs may dictate that a sampling procedure be employed) that information/education was provided to:
    a. parents (e.g., distributed materials, with an opportunity for parents to ask questions); and
    b. health care providers (e.g., via a program practitioner manual).
12. Document the effect of identification as screen positive on access to services and insurance[3].
13. Document monetary and other costs of diagnosis and follow-up (include impact on families).
14. Document that programs have a mechanism in place to provide for consumer input, as well as the rates of consumer complaints related to all parts of the program.
15. Document the use of a standing external multidisciplinary/advisory committee for program guidance that includes consumers.

**Transition Between Screening Program and Diagnostic/Follow-up Phase**

16. Educational materials should exist that clearly explain screen-negative results to parents and health care providers (including materials to guide their initial response to notification of a screen-positive infant).
17. Maintain a listing of qualified subspecialty providers available to confirm diagnoses, conduct follow-up testing of screen-positive infants, and manage treatment of those identified by screening.
18. Document the number of newborns with an identifiable medical home.[4]

**Diagnosis and Follow-up**

19. Integrate reporting and follow-up information systems, including communication with specialists and laboratories diagnosing conditions that are part of newborn screening:
    a. so that no child is lost to follow-up;
    b. to allow identification and communication back to programs of cases identified diagnostically (clinical, enzymatic, biochemical, or molecular confirmation for each test leading to the final diagnosis), but missed by screening programs; and
    c. to include screening laboratory and diagnostic follow-up laboratory identification and location to facilitate physician referral.

    [Note: An emerging issue is whether a newborn screening program should include diagnosis and follow-up in its fees. In addition, in developing referral networks, consideration will have to be given to which tests require such a network (e.g., metabolic) and which have more stable technologies (e.g., thyroid)]
20. Develop a QA system that includes
    a. total quality management (TQM)/continuous quality improvement (CQI);
    b. auditing; and
    c. documentation of corrective actions.

**Societal Outcome Goals**

21. Programs should collect outcome data to accrue knowledge about the natural history of conditions. For conditions for which there is a limited knowledge of the implications of results (e.g., ancillary information from MS/MS), there is the potential to enhance knowledge of implications through research and/or tracking of outcomes. Since such data collection is largely a research-based initiative, it may best be done as special studies.
    a. Identify individuals who might benefit from involvement in research or who should be more closely watched in a neonatal intensive care unit environment.

## Appendix 5

**HIPAA guidance for public health programs**

Recently, there have been significant changes to federal privacy regulations related to protected health information (PHI). On April 14, 2003, the federal privacy regulations (referred to here as the Privacy Rule) became effective as a result of HIPAA (45 CFR Parts 160 and 164).

These new regulations provide specific exemptions and allowances for public health activities and to those providing services associated with those activities. A work group of the expert group was asked to provide guidance regarding these regulations and their impact on the various participants in newborn screening program activities.

The Privacy Rule applies only to "covered entities" (health care plans such as HMOs; health care clearinghouses that assist providers with billing; or health care providers who transmit PHI in electronic format for financial or administrative activities [for which the Secretary of DHHS has established a format related to health care]). The goal is to protect confidential patient health, identifiable demographic information, and billing information. The Privacy Rule does not apply to employers, insurers, schools, or other entities, except to the extent that they perform activities as a covered entity. The rule does apply to federal, state, and local governments in their role as covered entities (e.g., through Medicare, Medicaid, the Indian Health Service).

HIPAA covers both the use and disclosure of PHI. Use is defined as "the sharing, employment, application, utilization, examination, or analysis of such information within an entity that maintains such information." Disclosure refers to "the release, transfer, provision of access to, or divulging in any other manner of information outside the entity holding the information." However, exceptions are made for public health activities. Newborn screening is mandated by law in all 50 states and the District of Columbia, with required reporting to relevant public entities and the patient's treatment team. It is beyond the scope of this document to describe each state's laws.[5]

A covered entity may use and disclose PHI without the consent or authorization of the individual for treatment, payment,

or health care operations. "Operations" include most routine activities of a covered entity. Research is not included in operations as defined by the regulations.

Uses and disclosures of PHI beyond treatment, payment, or health care operations are only lawful if 1) pursuant to a valid authorization; or 2) pursuant to an exception set out in the Privacy Rule.

PHI can be disclosed to third parties with an individual's written authorization. ("Individual" is defined in the regulations as a competent adult or a personal representative acting on behalf of an incompetent person.) For the purposes of newborn screening, the newborn is represented by parent(s) or a legal guardian.

State laws "serving a compelling need related to public health, safety or welfare" remain in effect after April 14, 2003. Specifically, state laws concerning the reporting of disease and the conduct of public health surveillance, investigation, or intervention remain in effect (45 CFR Section 160.203). Further, covered entities can disclose otherwise protected patient information for public health activities without prior notice to the individual or the signing of an authorization. Pursuant to section 164.512(a) and (b) of the regulations, covered entities may disclose information for public health surveillance, public health intervention, and other public health purposes. These provisions make it clear that state newborn screening and reporting laws and programs remain in effect.

Under the Privacy Rule, a covered entity may use or disclose PHI without consent, authorization, or an opportunity to agree or object by the patient where:

1. the use or disclosure is required by law (including a public health law such as a newborn screening law); or
2. the disclosure is to a public health authority authorized by law to receive the information for public health activities (164.512(a) and (b)); or
3. the disclosure is for treatment needs of the patient. Treatment includes provision, coordination, or management of health care and related services by one or more providers, including coordination and management by a provider with a third party.

The Privacy Rule permits public health reporting, but it does not require it. Reporting requirements are established by provisions of state and local laws.

There are two kinds of public health disclosures under the Privacy Rule—mandatory and permissive. Mandatory disclosures are those required by law, and the Privacy Rule places no limit on the amount of information disclosed. Section 164.512(b) also permits covered entities to disclose PHI to public health authorities and their authorized representatives for public health surveillance, investigations, and interventions. A "minimum necessary" requirement applies to "permissive" disclosures, thereby limiting such disclosures to the "minimum necessary to accomplish the intended purpose of the use, disclosure, or request" (Section 164.502 (b) (1.).

A "Public Health Newborn Screening Program" includes initial screening, QA, diagnosis, follow-up, contracts with academic laboratories and consultants, and management of the research uses of the stored data. A program must share data among state agencies, laboratories, physicians, and state- and Institutional Review Board (IRB)-approved researchers to fulfill the public health mandate. Because each state's program is run in different ways, each needs to consult with its advisors about its status as a "covered entity," "provider," or other public health-related status. For example, under the Privacy Rule, if data are collected as surveillance data under 164.512(b) by a public health authority authorized by law to collect or receive such information for the purpose of preventing or controlling disease, any subsequent use or disclosures are not required to comply with the Privacy Rule. State law may provide added protections. If the public health authority is also a covered entity, the Privacy Rule would apply for subsequent uses, for example, research (see discussion below).

Once screening has occurred, the results, the diagnosis, a care plan, and follow-up treatment can be transmitted to the laboratory, the public health department, and the physician(s) providing care. This is allowed under the regulations because of the public health mandate and because once a patient has received and acknowledged the Notice of Privacy Practices (a document that explains the patient's rights and the actions the provider will take to protect privacy), the PHI can be used and disclosed. The patient would receive a notice from the hospital where the birth occurred and from the primary care physician.

## Security

If PHI is transmitted electronically (which means by computer, not by phone or fax), transmission must be secure. The security conditions required are set forth in HIPAA security regulations found in relevant parts of 45 CFR Parts 160 and 164. Those regulations become effective April 21, 2005. They require adequate firewalls, encryption, password protection, and backup so that electronic transmissions can protect the confidentiality of the PHI.

## Research

Research conducted by state or federal programs as mandated by relevant law is permitted as a public health activity.

For research by private researchers or research not mandated by law (e.g., a prevalence study using identifiable names linked to DNA), the rules of research would apply. Research with human subjects conducted with federal funding (or involving researchers otherwise covered by federal law) is regulated by 45 CFR Part 46.

Because research is not considered to be part of treatment, payment, or operations, a researcher wishing to access PHI from a covered entity must either:

1. de-identify the PHI so that the patient cannot be determined. De-identification occurs once the following items are redacted from the data to be used by the researcher:
   - names;
   - all geographic subdivisions smaller than a state, including address, except for the initial 3 digits of a zip code

(there are special rules for zip codes containing 20,000 or fewer people;
- all dates, except the year including birth date;
- telephone number;
- fax number;
- electronic mail address;
- Social Security number;
- medical record number;
- health plan beneficiary number;
- account numbers;
- certificate/license numbers;
- vehicle identification and serial numbers;
- device identifiers and serial numbers;
- URLs;
- IP address numbers;
- biometric identifiers;
- full-face photos or comparable images; and
- any other unique identifying number, characteristic or code.

OR

2. have the patient authorize access to the PHI, unless a Privacy Board or an IRB waives the need for authorization in accordance with specific requirements designed to protect privacy. Those requirements include a finding that the research could not practicably be conducted without the waiver, that data will not be reused or disclosed to a third party, and that there is an adequate plan to protect privacy (164.512(i)).

OR

3. construct a Limited Data Set, where the data are provided to a researcher who has signed a Data Use Agreement. A Limited Data Set can include dates and geographic information, but not street addresses or other direct identifiers listed above. A Data Use Agreement establishes the permitted uses of the limited data set and says the researcher will not further use or disclose the information, will protect it, and will not identify or contact the individuals whose data are in the set.

For research using DNA derived from dried-bloodspots:

a. there must be de-identification, which can most easily be accomplished by simply snipping off a piece of the specimen and providing no other information; or
b. there must be parental or legal guardian written authorization on a Privacy Rule compliant form; or
c. there must be a waiver of the need for authorization properly granted by a Privacy Board or IRB; or
d. there must be a Limited Data Set containing only general geographic information and relevant dates, coupled with a data use agreement signed by the researcher (see privacyrulesandresearch.nih.gov/).

## Conclusion

Because newborn screening and related activities are permitted under 45 CFR Section 164.512 (a) and (b) and are required by state law, these activities and associated research can proceed under the Privacy Rule. The greatest challenge is to confront the often pervasive misinformation about the Privacy Rule that sometimes has been used to justify the nondisclosureof newborn screening and other public health information.