

Newborn Screening in the 21st Century: Current Status and Considerations

A White Paper from the Health Promotion and Prevention Committee American Association on Mental Retardation April 2, 2002

The purpose of this white paper is to inform the members of the American Association on Mental Retardation (AAMR) on the current status of newborn screening in this country and to discuss the controversies that presently exist. The specific goals are to: (a) raise awareness among AAMR members concerning issues related to newborn screening, (b) disseminate current information to assist members in making informed decisions, and (c) establish an initial point of discussion regarding newborn screening issues. It is important to note that genetic screening may occur at any age and may be conducted at various times in one's lifespan, from preconceptual to prenatal to newborn to when specific developmental/health problems arise. This white paper will only focus on the newborn period.

The first newborn screening test to be developed was phenylketonuria (PKU) and this test was initially mandated for use in every newborn in Massachusetts in 1963. The test to identify the presence of elevated plasma phenylalanine was developed by Robert Guthrie in 1961 after it was found that the primary symptom of mental retardation was prevented with a special diet, eliminating this amino acid. Pressure to mandate this screening test came from the National Association for Retarded Children (NARC, now **The Arc US**), the Children's Bureau, and the **Joseph P. Kennedy, Jr. Foundation**. From this time, the number of newborn screening tests grew as the tests were developed.

Currently, every state and U.S. territory mandates the number of newborn screening tests, and this number varies from three to eleven. There is no national standard. The most common inborn errors of metabolism being screened by states and territories include PKU, hypothyroidism, galactosemia, biotinidase deficiency, congenital hypothyroidism, and maple syrup urine disease. More recently, hemoglobinopathies, cystic fibrosis, and amino acid, organic acid, and fatty acid oxidation disorders have been added. Many states are also requiring infant hearing screening tests. The most recent compilation of state mandated screening tests is from 1998 (National Newborn Screening and Genetics Resource Center, 2001). This document also reveals the prevalence and incidences of commonly mandated inborn errors of metabolism per state and territory, summation of fees charged per state and territory, infant ages at initial and secondary testing, and the laboratories providing newborn screening services in the United States. The National Conference of State Legislators (2002) also maintains a website for current legislative action concerning newborn screening in each state and territory.

Determining the appropriate number of newborn screening tests to be mandated by each state has produced much controversy in recent years. A major reason for this was the advent of tandem mass spectrometry in the late 1980s. This instrument can measure various components of the blood, urine, or plasma in about two minutes for approximately 20-30 metabolic disorders (the most common disorders are listed in Table

1). Biotinidase deficiency and galactosemia cannot be screened by tandem mass spectrometry. The cost for tandem mass spectrometry testing is approximately \$25.00 and provides a cost-effective means for screening (Pollitt, 2001). This testing method was approved as a reasonable and cost-effective screening instrument by the American Association on Mental Retardation Board of Directors at their meeting in May, 2001.

Tandem mass spectrometry has greatly increased the efficiency and accuracy of these tests for diagnosis. For this to be true, this method must have analytic validity, clinical validity, clinical utility, and social consequences. These criteria can comprehensively ascertain the benefits and risks of genetic tests (Secretary's Advisory Committee on Genetic Testing, 2000). Analytic validity measures whether the test accurately measures what it is supposed to measure. Clinical validity "refers to the accuracy of the test in diagnosing or predicting risk for a health condition and is measured by the sensitivity, specificity, and predictive value of the test for a given health condition" (Secretary's Advisory Committee on Genetic Testing, 2000, p. 16). Clinical utility then becomes the discussion of the outcomes of both positive and negative findings. Social consequences involve the effect of the test results on the individual, their family, to society in general. All of these factors must be taken into consideration. In the case of tandem mass spectrometry, clinical validity has begun to be tested for the different health conditions covered under this method. Levy (1998), Seashore (1998), and Rashed, Rahbeeni, and Ozand (1999) present findings from research studies that indicate that in general, and for specific health conditions, there are fewer false positive results using tandem mass spectrometry and the method is cost-effective. Levy (1998) argued that more states have not changed to using this method because of political reasons (e.g., changing the laboratories where current newborn screening results are analyzed and generally, not wanting to alter current practice). Seashore (2000) discussed in detail the importance of considering false-negative and false-positive results, the impact of early newborn discharge after delivery on test accuracy, and the need for adequate education of health care professionals and the public about the newborn screening program. Hannon and Grosse (2001) present a comprehensive discussion of tandem mass spectrometry in their work group report to the National Center for Environmental Health, Centers for Disease Control and Prevention which included the recommendation that more testing is needed to determine analytic and clinical validity of this method for specific health conditions. They note that there is a trend for good clinical utility, but additional research is needed to account for all of the social consequences. Members of AAMR are encouraged to read their report on the *MMWR* web site if they are wishing further information on this method.

Controversy has arisen over this method due to (a) the identification of disorders for which we have very little information and have no current treatment, (b) the need for state-wide advisory committees to determine criteria for mandated screening, and (c) the need for ethical pilot studies to assess clinical utility of tandem mass spectrometry and the use and storage of the dried blood spots needed for screening. Each of these points will be discussed in more detail.

Health care professionals and agencies who focus on the needs of infants and children with mental retardation and developmental disabilities have classified the

disorders currently being tested and under consideration for testing in basically two categories: (a) treatable disorders requiring early identification for effective treatment and (b) conditions not currently treatable but in which identification would provide parents with information to plan for their child's quality and length of life and for future child-bearing decisions. The Human Genome Project has introduced much of the knowledge and technology to identify many of the conditions now being discussed that can be identified by tandem mass spectrometry. The March of Dimes Foundation has argued loudly that any test that might be available should be used to screen every newborn regardless of cost. Hannon and Grosse (2001) reported on a workshop that focused on tandem mass spectrometry and its use for screening metabolic disease (see also comments on page 2). The participants of this workshop held discussions on decision criteria, diagnostic protocols, laboratory methodology, quality assurance, program evaluation, and patient case management. The participants also delineated the importance of both short-term and long-term follow-up of infants identified. Their concerns involved around the need for further pilot studies to determine clinical utility, ascertainment of clinical heterogeneity in infants, mild and late-onset variants of the different disorders, and a better understanding of the conditions. Their recommendation was for further study. It should be noted that health care professionals should dialogue about the definition of "treatable conditions." The AAMR definition of mental retardation includes the discussion of social supports. This could be considered when discussing "treatable conditions," realizing the importance of early intervention for newborns with a positive screen.

Grosse and Gwinn (2001) reported that most states do not have a state advisory committee that is concerned with newborn screening in that state. Massachusetts has such a committee and in 1998 the members developed a set of criteria for selection of newborn screening tests:

- Consumer involvement in decision to mandate screening
- Availability of an accurate screening test
- Disorder is treatable and requires early treatment
- Significant, life-challenging risk of morbidity if disorder is untreated
- Reasonable price of screening test
- Significant prevalence of disorder
- Resources for and access to treatment and counseling
- Positive health benefits must outweigh risks and burdens
- Existence of mechanism for regular review of scientific and medical rationale (p. 124).

The Secretary's Advisory Committee on Genetic Testing (SACGT) (2002) published recommendations for national oversight of genetic tests requesting that the Centers for Disease Control and Prevention (CDC) head this effort. They also published another report (Secretary's Advisory Committee on Genetic Testing, 2001) that detailed conclusions and recommendations for a classification methodology. After extensive research and conversations with professionals, the public, and policy makers, the Committee decided that the development of a classification methodology for genetic tests

was not appropriate at this time. This is an evolving topic that bears surveillance as to the progress of a national system and/or delineation of recommended criteria by a federal agency, such as the CDC.

Determining the newborn screening tests to be mandated by a state or territory must be done with close attention to ethical research to determine their efficacy and cost-effectiveness. Hanson and Thomson (2000) identify that public burden for some health conditions may prompt mandated newborn screening tests, while others state that the tests should not be mandated to be completed, but mandated to be offered. This is a controversy that must be systematically contemplated, acted upon, and periodically evaluated. Another important issue is confidentiality of these test results. Many argue that confidentiality must be maintained at all levels, although some would argue that a “medical need-to-know” is sometimes necessary and a family member should be told. Planning for follow-up, patient management or treatment, and genetic counseling for parents must also be determined. Atkinson and associates (2001) stress that there needs to be sufficient scientific and medical evidence to justify the introduction of a new newborn screening test and that quality standards must be met. Grosse and Gwinn (2001) emphasized the need for population-based studies.

Another issue surrounds the need for parental consent for newborn screening. The Task Force on Genetic Testing coordinated by the Department of Energy and the National Institutes of Health in 1997 concluded that consent should be waived for those tests that have well-established validity and benefit, but required for those tests where the validity and utility are not well-established. Atkinson and associates (2001) discussed the concept of “informed dissent” in which parents are allowed to refuse screening for investigational tests after they receive information and counseling on that test. The Task Force on Newborn Screening formed from the Health Resources and Safety Administration (HRSA) and the American Academy of Pediatrics (AAP) in 2000 recommended that parents be allowed the right to refuse or dissent for any newborn screening test. In any case, parents need up-to-date information on the course of the health condition across the lifespan, the advantages and disadvantages of treatment, and the social, economic, and emotional effects of the condition on the individual and family. For example, the NIH Consensus Panel (2000) recently published a document on PKU providing much of this information. Further discussion is needed regarding the appropriate ethical protocols to be taken when providing newborn screening tests.

Another ethical issue surrounds the use and storage of blood spots that contain the DNA of newborns. Issues arise in regards to use, sample storage, ownership, and confidentiality. Policy must be determined for the protection of this private information.

In 2000, the Newborn Screen Task Force recommended that health professionals, the public, and public health agencies within each state or territory should:

- Better define public health responsibilities for federal and state public health agencies

- Develop and disseminate model state regulations to guide implementation of state newborn screening systems (including disease and test selection criteria)
- Develop and evaluate innovative testing technologies
- Design and apply minimum standards for newborn screening activities (e.g., sample collection, laboratory quality, sample storage, and information systems)
- Develop and disseminate model follow-up, diagnosis, and treatment guidelines and protocols for health professionals, and other participants in the newborn screening system
- Design and evaluate model systems of care with services and supports from infancy to adulthood that are consistent with national guidelines for children with special health care needs
- Design and evaluate tools and strategies to inform families and the general public more effectively
- Fund demonstration projects to evaluate technology, quality assurance, and health outcomes (p. 386).

Newborn screening is an important topic and must be weighed carefully by the members of the American Association on Mental Retardation (AAMR). It is important that members are informed of the conditions tested by the current newborn screening programs, the prevalence of the diseases, what tests are performed in their state, the validity and accuracy of the testing method, and the ethical issues surrounding newborn screening. This paper was written in an effort to inform the members of AAMR of the current status and issues surrounding this important public health program. Information on the specific diseases covered by newborn screening can be found on various websites, including the Arc, the March of Dimes Foundation, and in genetic textbooks. The members of the Health Promotion and Prevention Committee have discussed whether recommendations for AAMR should be given. At this point, we believe that it is important to be informed. We also believe that due to the dynamic nature of genetic knowledge at this date and the continuing work of the Secretary's Advisory Committee on Genetic Testing, specific guidelines and recommendations concerning newborn screening will come from this Committee in the future. In the meantime, this Committee will work to produce additional documents in future years to update the membership on this important topic.

References

- American Academy of Pediatrics. (2000). Serving the family from birth to the medical Home: A report from the Newborn Screening Task Force convened in Washington DC, May 10-11, 1999. *Pediatrics*, 106, 383-427.
- Atkinson, K., Zuckerman, B., Sharfstein, J. M., Levin, D., Blatt, R. J. R., & Koh, H. K. (2001). A public health response to emerging technology: Expansion of the Massachusetts Newborn Screening Program. *Public Health Reports*, 116, 122-131.
- Grosse, S., & Gwinn, M. (2001). Assisting states in assessing newborn screening options. *Public Health Reports*, 116, 169-172.
- Hannon, W. H., & Grosse, S. D. (2001). Using tandem mass spectrometry for metabolic disease screening among newborns. *MMWR*, 50 (RR03), 1-22.
- Hanson, J. W., & Thomson, E. J. (2000). Genetic testing in children: Ethical and social points to consider. *Pediatric Annals*, 29, 285-291.
- Holtzman, N. A., & Watson, M. S. (Eds.). *Promoting safe and effective genetic testing in the United States: Final report of the Task Force on Genetic Testing*. Retrieved January 25, 2002 from http://www.nhgri.nih.gov/ELSI/TFGT_final/.
- Howse, J. L., & Katz, M. (2000). The importance of newborn screening. *Pediatrics*, 106, 595.
- Levy, H. L. (1998). Newborn screening by tandem mass spectrometry: A new era. *Clinical Chemistry*, 12, 2401-2402.
- National Conference of State Legislators. (2002). *Maternal and child health. Newborn genetic and metabolic disease screening*. Retrieved January 25, 2002 from <http://www.ncsl.org/programs/health/screen.htm>.
- National Institutes of Health. (1997). Genetic testing for cystic fibrosis. NIH consensus statement. Retrieved January 25, 2002 from <http://test.nlm.gov/nih/cdc/www/106txt.html>.
- National newborn screening report – 1998*. (2001). Austin, TX: National Newborn Screening and Genetics Resource Center.
- Newborn Screening Task Force. (2000). Newborn screening: A blueprint for the future. *Pediatrics*, 106, 386-388.
- Phenylketonuria (PKU): Screening and management*. (2000, October 16-18), NIH Consensus Statement. 17 (3), 1-33.

- Pollitt, R. J. (2001). Newborn mass screening versus selective investigation: Benefits and costs. *Journal of Inherited Metabolic Diseases*, 24, 299-302.
- Rashed, M. S., Rahbeeni, Z., & Ozand, P. T. (1999). Application of electrospray tandem mass spectrometry to neonatal screening. *Seminars in Perinatology*, 23 (2), 183-193.
- Seashore, M. R. (2000). Genetic screening and the pediatrician. *Pediatric Annals*, 29, 272-276.
- Seashore, M. R. (1998). Tandem spectrometry in newborn screening. *Current Opinion in Pediatrics*, 10, 609-614.
- Secretary's Advisory Committee on Genetic Testing. (2001). *Development of a classification methodology for genetic tests: Conclusions and recommendations of the Secretary's Advisory Committee on Genetic Testing*. Retrieved January 25, 2002 from <http://www4.od.nih.gov/oba/sacgt.htm>.
- Secretary's Advisory Committee on Genetic Testing. (2000). *Enhancing the oversight of genetic tests: Recommendations of the SACGT*. Retrieved January 25, 2002 from <http://www4.od.nih.gov/oba/sacgt.htm>.

Table 1. Amino Acid, Organic Acid, and Fatty Acid Oxidation Disorders Tested by Tandem Mass Spectrometry

1. Argininemia
2. Argininosuccinic aciduria
3. B-ketothiolase deficiency
4. B-methyl crotonyl carboxylase deficiency
5. Carnitine palmitoyltransferase II (CPT) deficiency
6. Citrullinemia
7. Glutaric acidemia I
8. Glutaric acidemia II
9. HMG lyase deficiency
10. Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome
11. Isovaleric academia
12. Long-chain hydroxylacyl-CoA dehydrogenase deficiency (LCHAD)
13. Long-chain acyl-CoA dehydrogenase deficiency (LCAD)
14. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
15. Methylmalonic aciduria
16. Propionic acidemia
17. Short-chain acyl-CoA dehydrogenase deficiency (SCAD)
18. Tyrosinemia I
19. Tyrosinemia II
20. Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)