

Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children Summary of Inaugural Meeting

June 7-8, 2004
Washington, DC

Prepared for:

Maternal and Child Health Bureau
Health Resources and Services Administration
Rockville, MD

Prepared by:

Health Systems Research, Inc.
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2 July 2004

The Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was convened for its inaugural meeting at 9:05 A.M. on June 7, 2004, and was adjourned at 3:00 P.M. on June 8, 2004 at the Ronald Reagan Building and International Trade Center, Washington, D.C.

In accordance with the provisions of Public Law 92-463, the meeting was open to the public from 9:05 A.M., June 7, 2004 to 3:00 P.M., June 8, 2004.

Committee members present:

Dr. Duane Alexander**
Dr. William Becker
Dr. Amy Brower
Dr. Peter Coggins
Dr. Gregory Hawkins
Dr. Joe W. Gray
Dr. Rodney Howell
Dr. Piero Rinaldo
Dr. Coleen Boyle**
Dr. Peter van Dyck**
Dr. Stephen Edwards*
Dr. Jennifer Howse*
Dr. Reed Tuckson*

* Liaison Members

** Ex Officio

Staff of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children attending were:

Dr. Michele Lloyd-Puryear, Executive Secretary
LTJG Gilian Engelson, Administrative Associate

Members of the public who presented oral or written statements were:

Ms. Wendy Berry West, Ohio Sickle Cell and Health Association
Anthony A. McKinney, LysoPlex, LLC
Ms. Jill Fisch, Parent
Mr. Jim Kelly, Hunter's Hope Foundation
Ms. Jana Monaco, Organic Acidemia Association and the National Coalition for PKU & Allied Disorders
Dr. Philip Vaughn, Pediatrix Screening
Ms. Micki Gartzke, Parent
Dr. Mendel Tuchman, Society for Inherited Metabolic Disorders
Ms. Kathleen Rand Reed, The Rand Reed Group
Dr. Rebecca Buckley, Immune Deficiency Foundation
Ms. Teri Broadstreet, Parent (written public comment sent through the Honorable Howard Coble's office)

Welcome and Introductions

After **Dr. R. Rodney Howell, Committee Chairperson and Professor of Pediatrics at the University of Miami**, called the meeting to order, **Dennis Williams, Ph.D., M.A., Deputy Administrator, Health Resources and Services Administration (HRSA)**, offered greetings from HRSA Administrator Betty Duke and thanked attendees for participating in the first meeting of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (Committee). Dr. Williams also thanked Dr. Howell for serving as chairperson, and Peter van Dyck, M.D., M.P.H., M.S., Associate Administrator of the Maternal and Child Health Bureau (MCHB), HRSA, for serving as the HRSA representative for this Committee.

Dr. Williams noted that the life-threatening or disabling impacts of many heritable disorders can often be prevented if detected early in an individual's life. The charge of this Committee is to advise the Secretary of the Department of Health and Human Services (DHHS) on the most appropriate application of screenings, health services, and counseling to identify and treat a range of heritable disorders. The national guidelines that the Committee recommends to the Secretary will help DHHS officials develop policies to encourage advances on many crucial issues among their partners and State and local public health agencies. These include improving the quality of screening programs, promoting equal access to genetic testing by all newborns and their families, and standardizing treatment and follow up from State to State.

The Department of Health and Human Services, Dr. Williams said, has supported the development of newborn screening programs since the 1960s, primarily through the activities of MCHB, and researchers at the National Institute of Child Health and Human Development (NICHD). The Center for Disease Control and Prevention's (CDC's) Newborn Screening Quality Assurance Program has improved quality practices among state laboratories, and its national Center on Birth Defects and Developmental Disabilities provides expertise in the areas of epidemiologic surveillance and evaluation.

More recently, the Agency for Healthcare Research and Quality (AHRQ) has supported research that helps health care professionals use advances in genetics to improve the care they provide. Strengthening the scientific basis for newborn screening is one way the federal government can support State newborn screening programs, and HRSA has been a leader in translating the findings of genetic science into practice.

The discretionary grants portion of HRSA's Maternal and Child Health Block Grant Program is the primary source of Federal funding of newborn and other genetic screening, counseling, and information projects. In 2000, the MCHB funded American Academy of Pediatrics Task Force report on newborn screening and genetic testing, "Serving the Family from Birth to the Medical Home" was released. In 2002, a HRSA genetics workgroup, consisting of representatives of all of HRSA's bureaus and offices and chaired by Dr. Sam Shekar, HRSA Associate Administrator for Primary Care, began to inventory all genetics-related activities across the agency. The group was instructed to develop a strategic plan for future genetic activities and to strengthen partnerships to advance genetic education and service. The workgroup's report is expected to be released soon.

HRSA also trains health care and public health professionals in genetics via the Genetics in Primary Care project, which targets the next generation of health care professionals by introducing genetics to students in health professions, and through the new Family History project—in partnership with the March of Dimes and the Genetic Alliance—that allows HRSA to educate consumers so that they understand the benefits, risks, and limitations of genetic testing.

Dr. Williams concluded by cautioning that advances in genetic testing and understanding are leading us into a future in which scientific gains strain against the moral and legal boundaries that have guided us up until now. He noted that the role of the Committee is to help the Secretary and the Nation understand these challenges and the choices that await us.

Charge to the Committee

Dr. Howell then reviewed the charge to the Committee, the members of which were appointed by Secretary Thompson. Title XXVI of the Children's Health Act of 2000 authorized the establishment of the Committee—the Committee has to make recommendations to the Secretary, if they become regular practice in the United States, will create the opportunity of saving children's lives.

Dr. Howell then outlined a few of the key issues that the Committee will address. The Committee will review and recommend improvements in the national newborn screening and childhood screening programs. The Committee also will provide advice and recommendations to the Secretary concerning grants and projects awarded or funded under Section 1109 of the Public Health Service Act. This section of the Public Health Service Act authorizes grant awards to enhance, improve, or expand the ability of States and local public health agencies to provide screening, counseling, or health care services to newborns or children who have or who are at risk for having heritable disorders. The Committee also is charged with providing technical information to the Secretary for the development of policies and priorities for the administration of grants under Section 1109 of the Public Health Service Act, and to provide such recommendations, advice, or information as may be necessary to expand and improve the ability of the Secretary to reduce the mortality or morbidity related to heritable disorders in newborns and children.

Dr. Michele Lloyd-Puryear, Committee Executive Secretary, then reviewed the history of the Committee. She noted that membership is limited to 15 members and outlined the specific expertise required to be represented on the panel. MCHB structured the Committee to include both voting and non-voting members. In addition, several different types of members comprise the Committee. First are representatives of other advisory Committees—the Secretary's Advisory Committee on Infant Mortality and the Secretary's Advisory Committee on Genetics, Health, and Society. The members representing these advisory Committees do not vote. The Committee also includes representatives of the American Academy of Pediatrics, and of the March of Dimes (representing the public at large); these members also do not vote. The remaining members vote, including the representatives of the four Federal agencies on the Committee—the AHRQ, CDC, HRSA, and the National Institutes of Health (NIH).

Delivering Genetic Services to Children in a Clinical Setting

Dr. Howell began by stating that genetic services have been an integral part of the medical care of children for more than 40 years. Those services have focused on visible clinical features, such as Down's syndrome and dysmorphism—diagnoses supported by increasingly sophisticated chromosomal studies and relatively simple single-gene defects that have commonly been detected through newborn screening, such as biochemical or metabolic abnormalities.

Dr. Howell reviewed the history of children's genetic services, beginning with the publication of Archibald E. Garrod's *Inborn Errors of Metabolism*. Garrod's book focused on visual data, and his visual inspections were corroborated by relatively simple chemistries that were available in the early 20th Century. Dr. Howell went on to highlight several disorders, such as alkaptonuria, that were explained by Garrod and later backed up by biochemical studies.

The next phase in the evolution of clinical genetics and biochemical genetics in children started with the simple screening tests that were used 35 to 40 years ago. Children who had special conditions or abnormalities such as mental retardation commonly received simple urine tests to see if there was anything in the urine that gave a clue to the diagnosis. Around that time, Robert Guthrie developed a simple screening test using dried blood spots in the diagnosis of phenylketonuria.

Dr. Howell reviewed the criteria used at that time for the mass screening of all newborn infants:

- The disorder should be treatable.
- The screening program should be administratively feasible.
- Methods should be simple, quick, inexpensive, and reliable.
- The program should be justified on economic grounds.

At the time of the development of the dried blood spot test, treatment for a disease was considered to be very specific, a concept that “you could get your hands around,” such as a diet

or medication, rather than a complex treatment. However, tandem mass spectrometry and other high-throughput genetic testing have changed how we look at inborn errors of metabolism, and the practice of newborn screening is expanding rapidly. These technologies have raised even more sophisticated issues. For example, conditions have been identified about which we have little data regarding their natural histories and the treatment. Another challenge for the researchers is that relatively few health care professionals in the United States are available with the expertise to follow up, diagnose, and treat patients with some of these uncommon conditions.

In addition to newborn screening, the Human Genome Project (HGP) has ushered in the era of predictive medicine and created an enormous opportunity for prevention. Dr. Howell briefly reviewed what we have learned thus far from HGP. The goal of HGP was to map and sequence the human genome, and after the completion of the sequence, the recent focus has been on sequencing the genomes of model organisms. Comparisons with other organisms, such as the mustard weed, the fly, and the worm, have shown that the human genome has more genes than other organisms, but not as many as scientists thought originally. However, humans have considerably more proteins than the organisms listed above, and the way that genetic information is used in humans is vastly more complicated, which will pose difficulties as scientists look at gene sequences to try to predict health outcomes. The public availability of the data emerging from HGP has stimulated technology development, as well as significant discussions of the ethical, legal, and social issues associated with genetic advances.

Dr. Howell then discussed the emerging scientific/medical fields that have resulted from genetic advances, including transcriptomics (the study of RNA transcripts), proteomics (the study of all the proteins in the cell) and metabolomics (the study of metabolomes—all of the small molecules within the cell). Combined, these fields will provide information about all of our genes, proteins, and RNA and create a complete picture of a fully functioning assembly of the human organism.

The discovery of the specific genes that underlie genetic defects are dramatically enhancing diagnosis. One of the areas that has undergone an enormous explosion in technology has been cytogenetics, which permits very sophisticated testing for small gene deletions, and diagnose important clinical conditions in childhood accurately. Dr. Howell used several case studies of

diseases, such as Cornelia de Lange syndrome, Pompe's disease, and Krabbe's disease, to illustrate how recent genetic advances are helping children who suffer from those diseases.

Another emerging field of genetic study is pharmacogenetics. The problem of adverse drug reactions is increasing in the United States; in fact, some data has indicated that it causes more deaths than pneumonia and diabetes. Although much is known about polymorphisms and how they might affect metabolism reactions to drugs at times remain unpredictable. Dr. Howell used the case of a mitochondrial mutation that causes a rare adverse reaction, ototoxicity (deafness), in response to a drug commonly used in the newborn nursery, particularly in premature infants who are diagnosed with sepsis. Dr. Howell illustrated the theory that with a very rapid test for that mutation, children could be screened before that drug is used.

Another issue that the Committee must address is testing for adult onset disorders in children, a problem about which the American Academy of Pediatrics has issued a specific comment. The Academy's recommendation is that you do not test children unless there is an immediate medical benefit, or if there is a benefit to another family member and no other recognized harm to that minor.

How conditions are diagnosed is changing dramatically. In addition to making a visual diagnosis, or measuring the patient's features, many more accurate diagnostic tests are available. Scientists also are learning that some conditions are considerably more variable and complicated than originally thought, because of varying expressions of disease genes.

Dr. Howell stated that over time, the challenges that some of these discoveries present will be addressed, including the education of professionals, which will be necessary for the public to take the best advantage of emerging genetic discoveries.

Committee members then discussed Dr. Howell's presentation, raising the issue of costs, especially when there are 43 million Americans who are uninsured: How do we best use limited resources? Dr. Howell pointed out the economics of scale when using tandem mass spectrometry—once you decide to use the technology to test for one disorder, the incremental cost to examine other disorders is modest. Some of the treatments are inexpensive, such as

biotinidase, while others, such as the treatment for lysosomal enzyme disorders, although life-saving, are more expensive to treat. These diseases, however, are rare, which prevents the costs of treatments from reaching crisis proportions in the population.

Two levels of economics must be considered when reviewing newborn and childhood screening—both at the population and individual family levels. No matter how rare the disease, it is devastating to that particular family, and the results can be life changing and costly, including loss of productivity and the amount of time spent looking for a diagnosis. In light of the economics of the treatment and the economics of the diagnostic costs for the individuals and the society in terms of health care cost increases, the Committee must consider the issues for public health, and State and local governments, as they try to decide how to best use their resources.

Committee members then spent some time clarifying their charge—whether or not they are to make recommendations in terms of public health or clinical practice. They agreed that the charge was broad, especially since newborn screening and clinical genetics in particular bring public health and clinical practice together. A lot of the issues that have been discussed fall somewhere between appropriate clinical practice and mandated public health screening, and the Committee is not limited in how it structures its recommendations.

Committee members also discussed briefly the issues of genetic counseling and the importance of the public understanding of the impact that genetics will have on their lives, especially those families that include members who suffer from a genetic condition. Genetic professionals who are knowledgeable about each disease that is screened must be available to the general public.

State of the States: Newborn Screening—Challenges and Opportunities

Dr. Marie Y. Mann then gave an overview of state newborn screening programs. She noted that the term "newborn screening" could mean newborn hearing screening, which screens for congenital hearing loss, or the more traditional biochemical screening for inherited and congenital conditions. For the purpose of her presentation, newborn screening would refer to the traditional biochemical screening.

Newborn screening is recognized as an essential public health program that has been lauded as an effective strategy for preventing significant morbidity and mortality in those infants with certain genetic or congenital. It also is a complex system that is dependent on many individuals and organizations, including the family members of the affected newborns, as well as myriad program officials, laboratory and follow-up professionals, and the primary subspecialty care clinicians who care for these infants. Policymakers, manufacturers, and the general public also are involved.

Newborn screening began in the early 1960s, when Robert Guthrie showed that a blood sample from the newborn could be absorbed and dried onto a standardized filter paper and that this sample could be analyzed for biochemical markers of metabolic disorders, such as phenylketonuria (PKU). However, it took the lobbying efforts of parents to convince health policymakers that this method could be used to screen newborns routinely. In 1965, the American Academy of Pediatrics Committee on the Fetus and Newborn recommended a newborn screening blood test for PKU for all newborns. Within a few years, most States had passed legislation mandating PKU screening. By 1973, 43 States had formal statutes.

Over the next decade, other filter-paper tests became available, for testing for such diseases and conditions as congenital hypothyroidism, congenital adrenal hyperplasia, and sickle cell anemia. With improvement in technological tests—such as automated specimen preparation, testing, and data handling systems—the program expanded to test for other disorders, such as congenital hypothyroidism. As the number of conditions for screening increased, the cumulative risk of being diagnosed with one of the conditions also increased. And so with congenital hypothyroidism being the condition of higher incidence, when hypothyroidism screening was added to the newborn screening program, cost effectiveness improved. This was important, because as programs had to justify themselves, their existence, and their spending, the State legislatures expected the programs to be self-supporting.

Throughout the 1980s, these programs continued to expand, and this expansion was assisted by computerized data management and record keeping that accommodated the increased testing volume, as well as the required follow up. Toward the end of the 1980s and into the early 1990s,

the ability to extract DNA from dried blood spots allowed for genotypic confirmation of sickle cell anemia. Subsequently, researchers discovered that DNA extraction could be used as a secondary tier for cystic fibrosis screening. Around this time, advances were being made in mass spectrometry technology, so during the early 1990s, the technique of linking two mass spectrometers in tandem was applied to newborn screening. Tandem mass spectrometry allows the simultaneous detection of multiple conditions, including organic acid, amino acid, and fatty acid oxidation disorders. With this new technology, public pressure to expand the programs increased, and the conditions to be screened increase in number.

The expansion of many of these programs has been the dramatic result of this work. Meanwhile, the equipment and procedures for screening newborns for hearing loss also were refined. Newborn hearing screening is now mandated in most States; however, unfortunately because many of the newborn hearing screening programs have been developed independent of the blood spot screening programs, the two often are not well linked. There is increasing interest in linking the two screening programs, as well as linking these programs with related newborn and child public health programs, such as birth registration, and immunization. Such linkage may be facilitated by data linkage and integration, keeping in mind the need to preserve and respect privacy and confidentiality of those involved. Programs also are examining the issue of storage of samples, as well as the impact of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) on the operations of the programs.

Dr. Mann then reviewed what a typical system looks like. The system is complex, and the components of this system need to be well coordinated for the system to function optimally. The system begins with screening, which involves sample collection, submission, and transportation to the laboratory and the testing itself. The results are then sent to the appropriate places Such as to the pediatrician. If the results are such additional testing is warranted, the family is brought back, and the child is retested. When a result is positive, the program must ensure that the child receives the appropriate follow up, appropriate testing, retesting if necessary, and referral for diagnostic testing. This diagnosis must be confirmed, and if it indeed is confirmed, then the child is referred to the appropriate subspecialist, and the family receives counseling, if needed.

The program would not be complete without continuous monitoring, as well as evaluation of the effectiveness of the program. Overlaying this system is essential education involving pretesting education for the families, the parents, and the expectant families, as well as the education of the hospital staff and personnel, and continuing education of the laboratory and program staff, the clinicians responsible for the care of the newborns, and the various policymakers and payers. Dr. Mann urged Committee members to remember that the system must be considered in its entirety to remain efficient and effective.

In 2002, at the request of Senators Dodd and DeWine, the General Accounting Office (GAO) was asked to examine the U.S. newborn screening programs. Some of the findings from the report were released in a March, 2003 report, which Dr. Mann summarized. Fifty-one States and the District of Columbia mandate newborn screening. Three of the programs require consent for the testing, and those are Maryland, WY, and the District of Columbia. Although most programs allow dissent, a few do not permit dissent for any reason. Eight programs mandate two separate screens, a screening during the newborn period and a second screen between 2 to 4 weeks of age. Several other States do not mandate the two screenings but strongly suggest that a second screening be performed.

Eight programs do not charge a fee for the newborn screening, but for others, the fee can be as high as \$70, excluding hospital and administrative costs. The amount of Medicaid reimbursements varies widely, with about one-third of all births being Medicaid. The storage time and protocols for accessing and using residual blood spots remain after testing varies widely.

Dr. Mann then reviewed the status of newborn screening in the country, beginning with the most commonly screened conditions in the United States, and the number of States screening for them. Currently all States and the District of Columbia screen for PKU, congenital hypothyroidism, and galactosemia; for other screened conditions, such as sickle cell diseases, congenital adrenal hyperplasia, biotinidase, maple syrup urine diseases, homocystinuria, medium-chain acyl-CoA dehydrogenase, but considerable variation among States exists. Only a few States currently mandate cystic fibrosis screening; even fewer screen for infectious diseases; and only the District of Columbia mandates screening for glucose-6-phosphate dehydrogenase, G6PD deficiency.

In summary, one State screens only for three disorders, and other States screen for more than 30.

Not only do the States vary in the number of conditions screened, but they also vary in other ways. One significant variation is the entity that performs the laboratory analyses. For example, Oregon's state laboratory conducts the testing for four other States. Massachusetts is another state lab that conducting the testing for other States in their region. Although most States use their own public health laboratory to conduct the laboratory analysis, some contract out that testing to other state or commercial labs.

Shortly after the HRSA funded-Council of Regional Networks (CORN) for Genetic Services came into existence in the 1980s, it began collecting newborn screening information from the State. With the dissolution of CORN in the late 1990s, this information-gathering activity was assumed by the National Newborn Screening and Genetics Resource Center. Dr. Mann summarized 10 years of data, listing conditions in order of prevalence. Sickle cell disease is the most prevalent condition, according to the data that have been recorded over the 10-year period, and homocystinuria is the rarest.

Dr. Mann then reviewed how decisions and regarding newborn screening are made. She noted that there is no Federal mandate—rather, newborn screening is a state-mandated public health activity, and as noted by the GAO, every State has enacted a law mandating screening. Sometimes, State law defines and specifies the conditions to be screened, as well as who is going to be doing this testing. Policies generally are made by the state health officers, as well as the state boards of health, and the state advisory Committees. All but two States have standing advisory Committees. Decisions about newborn screening policies are influenced by the interests of the various stakeholders, as well as the costs and benefits associated with screening, and the scientific evidence of such screening. Local politics, economics, and culture exert tremendous influence on these decisions as well.

Historically, the formal groups that periodically have made recommendations have provided the framework for much of the decision making in newborn screening policy. In the 1960s the World Health Organization (WHO) Scientific Group for Inborn Errors of Metabolism made recommendations, which resulted in Wilson and Jungner's criteria for population screening. They

identified 10 criteria, focusing on treatable disorders, affecting a significant population, that would have cost-effective outcomes. In 1975 the National Academy of Sciences also reviewed genetic screening. It made several recommendations in establishing some fundamental principles for genetic testing, as well as some guidelines for newborn screenings. These guidelines, however, differ very little from the WHO recommendations—the recommendations suggest that under controlled conditions, screening is appropriate, and that the responsibility for screening should reside in an agency representing both the public and health professions, and that there should be extensive public and professional education and involvement. They suggest that screening should not be mandatory, and privacy should be protected. If mandated, they recommend that there be a formal body to provide the structure for such screening, and that research should be conducted in an ethical manner to support decisions.

In 1998, HRSA's MCHB funded the American Academy of Pediatrics to convene a national Task Force on newborn screening, chaired by Drs. Edward McCabe and Thomas Tonniges. This AAP task force was jointly sponsored by a number of Federal agencies. The Task Force members represented individuals who operate programs, conduct research, persons who functioned within that system, and those who were affected by the system. Task Force findings and recommendations were published in August of 2000. These recommendations were based on the following fundamental principles:

- Infants should benefit from and be protected by newborn screening programs.
- Public health agencies should assume responsibility for oversight of newborn screening systems.
- Standards and guidelines for newborn screening should be more consistently applied, because greater uniformity would benefit families, professionals, and public health agencies
- Newborn screening systems should link to a medical home.

In conducting its work, the task force divided up into five workgroups, which made recommendations in several key areas, including public health infrastructure, public and professional involvement, surveillance and research, as well as financing. Finally, the task force prepared to recommend an agenda for action that involved public health partnering with health

professionals and consumers. The action agenda would model regulations for newborn screening systems, define Federal and State responsibility, define minimum standards for newborn screening, model guidelines and protocols for professionals, model systems of care from infancy to adulthood, design strategies to inform and involve families and the general public, and demonstration projects to evaluate technology, quality assurance, and health outcomes. Subsequent to the Task Force report, various congressional directives were made, where a Committee urged the availability and accessibility of newborn screening service to apply to public health recommendations for expansion of effective strategies. It directed that HRSA, in collaboration with CDC and NIH, encourage implementation of a strategy for evaluating and expanding newborn screening programs, and that tangible steps be taken to protect patient privacy and to avert discrimination based upon information obtained via screenings. In addition to congressional interest, Federal agencies also have been actively engaged in various activities that support newborn screening.

In 2000, the March of Dimes made a recommendation that all newborns should be screened for nine conditions as well as for congenital hearing loss. Since then, public interest has remained high, and in 2002, a Senate Committee meeting provided a forum from which individuals had the opportunity to make presentations.

One educational training activity that has been jointly supported by HRSA, CDC, the HRSA funded-National Newborn Screening and Genetics Resource Center, and the Association of Public Health Laboratories is designed to meet the needs of State programs that were implementing tandem mass spectrometry. The activity provided a one-week intensive course on the basis of tandem mass spectrometry methods interpretations that has been conducted at Duke, as well as at the Institute for Metabolic Disease at Baylor University. These programs have been designed to fill the training gaps for the States.

With continued funding from HRSA, the National Newborn Screening and Genetics Resource Center continues to send expert teams to States that request review and consultation. The team is made up of members who are experts in laboratory follow up, administration, quality assurance, and clinical care, to address specific program needs of the State programs. Since 1987, more than 22 States have requested such visits. A limited external evaluation of this activity found

overwhelmingly favorable response by the States visited. The National Newborn Screening and Genetics Resource Center, located at the University of Texas Health Science Center in San Antonio, also provides genetics and newborn screening information online. The information includes program links and testing summaries for the various programs, information about individual State newborn screening programs, as well as State genetics plans, and a searchable genetics education materials database, as well as other reports of regional and national significance.

In summary, Dr. Mann stated that of the approximately 4.1 million babies born annually in the United States, almost all are screened during the newborn period for a number of genetic and congenital conditions, and yearly approximately 4,000 of these newborns are found to have one of those conditions. In recent years, increasing differences among the States' screening programs have resulted in more than 1,000 newborns with detectable conditions may go undetected, because they are not screened for all the conditions for which tests are currently available. There is Federal and State interest in improving these programs to improve the equity between the programs, and although no national mandate exists, there is national interest in expanding newborn screening programs. Some of the challenges include the issue of financing and reimbursement for laboratory services, as well as for referral and follow up, and the long-term care of these infants; the availability of expertise, both at the laboratory level and the clinical level; and education and communication with all involved in the system.

Committee members asked Dr. Mann whether clear science is available for all currently available tests that indicate when that they should be performed and whether variation in States is due to competing views of what types of tests should be performed, or unclear science. Where do we turn for consensus on the best science available and for guidelines regarding what States should do? Dr. Mann reiterated that HRSA's contract with the American College of Medical Genetics (ACMG) will address one of those action items from the American Academy of Pediatrics Task Force to examine the science behind available tests and develop a mechanism by which conditions can be assessed based on the available scientific and clinical evidence before being added to screening panels. Dr. Therrell noted that some national guidelines—not federally mandated—were developed over the years of conducting reviews of State programs. The

national guidelines are interpreted differently by different programs. Each State develops its own guidelines, and it is usually the responsibility of the advisory Committee to develop them.

Dr. Therrell noted that there is a *Catch-22* related to the science, because in some cases, “if you don't do the screening, you don't get the science,” and we haven't done the screening because there weren't treatments.

Committee members also discussed whether they can recommend a Federal mandate for conditions to screen, and whether the States are ready for a Federal mandate. Dr. Van Dyck cautioned that terms such as mandates, guidelines, and standards are different, and each has different implications for States.

Committee members also recognized that there are activities going on outside of the recommendations of this Committee. There are commercial companies advertising over the radio about available tests. Questions also have been raised about the use of the testing and about whether patients who are covered by public programs should have access to the same sort of testing as patients who are covered by private insurance. All of these issues create a complex dilemma.

Federal Agency and Liaison Briefings U.S. Preventive Services (USPS) Task Force *Agency for Healthcare Research and Quality*

Elizabeth Edgerton, M.D., M.P.H., represented the USPSTF as the new Director of Clinical Prevention. Dr. Edgerton explained that AHRQ has identified 10 focus areas related to the Agency's mission and that these areas encompass quality care, safety, and improving health outcomes among Americans. The prevention portfolio at AHRQ oversees both the USPSTF, and also the dissemination of these findings at the patient and provider level.

Dr. Edgerton gave Committee members an overview of the methodology of the Task Force, in order to help them understand how one group approaches some of these same questions. The USPS Task Force was modeled after the Canadian Task Force, and was established in 1984. Over time, it has developed recommendations regarding around health care issues that are

relevant to primary care physicians. Currently it has a rotating board that participates for a term of 3 years.

The recommendations of the USPSTF are founded on evidence-based medicine for preventative health services used in the primary care setting. It looks at health outcome issues that relate to screening tests, counseling, and chemoprevention. Some of the relevant topics it has addressed are congenital hypothyroidism, Down syndrome, sickle cell hemoglobinopathies, neural tube defects, PKU, and newborn hearing screening.

The USPSTF is an independent panel of experts that includes primary care physicians, family practitioners, internists, pediatricians, experts in behavioral science, and experts in methodology. It also uses evidence practice centers in the systematic review of the evidence, as well as Federal and private organizations as expert partners to review the recommendations. Its goal is to provide impartial assessment of the existing evidence, and although this evidence evaluation is examined apart from any Federal agency, it is supported by AHRQ in the sense that it represents the mission to enhance the quality, appropriateness, and effectiveness of health care services.

Federal guidelines often fall into two categories: formal consensus or expert panels and those that are evidence-based. The USPSTF employs an evidence-based approach, which can sometimes cause concern when a decision needs to be made, and the USPSTF has concluded that not evidence exists. Dr. Edgerton reviewed the process used by the USPSTF, starting with topic selection, development of questions, a systematic review of the literature (including an assessment of internal and external validity, effectiveness, benefit, and a summary of results in narrative and table format), then recommendations and rationale. A published methodology regarding systematic evidence reviews and the engagement of expert opinion to consider the results of these reviews has been developed. The USPSTF issues recommendations in the form of letter grades or insufficient evidence. A finding of insufficient evidence often suggests a potential research agenda. Dr. Edgerton urged the Committee to consider what types of outcomes will be important for them to assess going forward with their work—whether it is identification, improved quality of life, or improved morbidity/mortality.

One of the important issues that the USPSTF as well as the Committee must address is the issue of efficacy versus effectiveness. The USPSTF recommendations are supposed to consider real-world settings. Benefits often decrease as risk increases, and interventions are implemented in real-world versus the trial setting. Again, requiring effectiveness data may seem too limiting and inconsistent with medical practice, but Dr. Edgerton explained that this is the methodology and the standards of the USPSTF. Dr. Edgerton also identified the challenge in assessing the magnitude of the net benefit and noted that no explicit criterion for magnitude exists. The USPSTF uses outcome tables to illustrate tradeoffs.

Dr. Edgerton also addressed the challenges of pediatrics. What are the health outcomes to mark the benefit of genetic testing? Outcomes can be biochemical, school performance, interaction with family and peers, and knowledge of the child's condition by parents, etc.

Committee members asked whether they would be able to obtain a list of the critical issues considered by the USPSTF. The Committee also suggested that certain topics be examined by the USPSTF.

Centers for Disease Control and Prevention

Colleen Boyle, Ph.D., Associate Director of the Science and Public Health Team at the CDC, presented CDC's activities in newborn screening, which are distributed across four groups at the CDC—the National Center on Birth Defects and Developmental Disabilities, and the Office of Genomics and Public Health, the laboratory education group, and the Newborn Quality Assurance Screening Laboratory. These activities began out of the need to improve the science base for newborn screening. CDC's activities primarily encompass the areas of surveillance, long-term follow up, and epidemiologic studies that generally are developed from surveillance and monitoring programs, and laboratory quality control and standards.

In terms of surveillance and long-term follow up with regard to newborn screening, the CDC is examining the issue of clinical utility, to try to understand the long-term impact on children and their families. Their mission is to ensure that every State and Territory has a complete early hearing detection and intervention, tracking, and surveillance program. The reason for

developing the data system is to ensure that children are followed through early identification, via screening, diagnosis, and intervention.

CDC has funded 32 State surveillance and tracking programs. These States provide CDC with data to help answer a number of questions in relationship to clinical utility, the implications of the program for various ethnic minority groups, or other questions that arise. CDC also has a number of research programs to address issues such as cost analysis, quality of life in Utah, and the contribution of the cytomegalovirus to congenital hearing loss. They also are looking at family and psychological issues, genetic services issues in North Carolina, long-term outcomes in Hawaii, a family satisfaction collaborative project in Colorado and Massachusetts, and a more detailed etiologic genetic study that is based in four locations in the United States. They are interested in developing long-term follow-up programming for blood spot and MS/MS screening, and currently are running pilot programs in Oregon, Idaho, and Iowa. These programs are funded to develop a medical records abstraction system for long-term follow up of infants identified through MS/MS screening, in the hopes of developing a tracking system that easily can be adapted by other State programs. Another project in Colorado is investigating integrating newborn screening programs into one database, linking hearing, metabolic screening, and screening for hemoglobinopathies.

In the area of epidemiology, the CDC has conducted a number of different activities. Some of them are based on data that have been collected on State levels, and others are evaluations of the evidence. CDC has conducted a number of scientific evidence reviews of quantitative evaluations, including screening for cystic fibrosis and muscular dystrophy, as well as maternal hypothyroidism. CDC scientists also have published an article in the *Morbidity and Mortality Weekly Report* regarding the contribution of select metabolic disorders to unexpected early childhood deaths, finding that about 1 percent of children who died under the age of three actually had an undiagnosed fatty acid oxidation disorder, or organic acidemia.

The Office of Genomics and Public Health (OGPH) also is interested in the idea of using newborn dried blood spots for epidemiologic and other public health purposes, and has held a series of discussions over the last couple of years regarding the use of stored newborn dried blood spot specimens, including discussions of the implications, both in terms of their utility for newborn screening , assessment of new technology, and laboratory quality-control issues. Dried

blood spots can provide a “gold mine” in terms of public health epidemiological research, and there are other applications as well. A recent survey conducted in concert with the Association of Public Health Laboratories found that 40 percent of responding States stored spots for more than 12 months. More than 80 percent favored storage of identifiable spots at either a state or regional level. But importantly, 20 percent of the responding States, which represent about 2 million annual births, would consider participating in an anonymous multistate survey, whether it be looking at the prevalence of specific genetic markers or other factors representing utility and potential, at least from a research perspective, in trying to answer some of the questions that the Committee will develop.

The OGPB has also used the National Center for Health Statistics NHANES III DNA databank to examine the prevalence of genes of public health significance—more than 87 variants of 57 genes will be examined in this study.

CDC also has developed a Newborn Screening Quality Assurance Program specifically for dried blood spots that addresses more than 35 disorders and includes close to 400 laboratories in 35 countries that are now enrolled in newborn screening quality assurance and proficiency testing programs. This will help standardize testing from both within the United States, as well as from outside. The types of activities or services provided by this program include filter-paper quality control, provision of reference materials, proficiency testing, and consultation. The major partner for this activity is the Association of Public Health Laboratories. In terms of research and development, the laboratory is examining genotype proficiency testing for some of the newborn screening conditions on the horizon, including cystic fibrosis and MCAD. CDC also has a number of projects related to genetic markers, such as one for Type I diabetes, and other to the impact of early identification and treatment in terms of long-term outcomes for children. The laboratory and training group also is involved in training courses for laboratory personnel for newborn screening, such as MS/MS, as well as quality assurance.

After Dr. Boyle’s presentation, Committee members discussed a number of issues, including whether anyone at the level of the Secretary's office is responsible for examining integrational coordination of the recommendations arising from various Federal Committees, or the information, knowledge, and the behavior related to newborn screening activities, because the

previous presentations indicate that they are operating independently of one another without an overall strategic plan, relying instead on “friendly collaboration.”

Committee members also discussed the absence of large population-based studies. NIH has been planning the National Children's Study, which will be a large population-based study of about 100,000 pregnancies. A family genome study from NIH has been discussed as well. CDC is overseeing a number of population-based studies that include biological samples, and focus on specific conditions like birth defects, diabetes, cancer, or heart disease.

Committee members discussed the issue of communication, not just between Federal agencies, but also among all professionals involved in these activities. Dr. Boyle stated that CDC is just beginning to reach out to professional organizations, to take advantage of collective knowledge, and to work through those organizations to research some of the science. A model for this type of collaboration exists in the National Vaccine Program Office, which was used in the last President's childhood immunization initiative and included representatives from a variety of agencies who coordinated an approach similar to that suggested by several Committee members. Dr. Puryear noted that the Committee is able to add representatives from Centers for Medicare and Medicaid Services, the Food and Drug Administration, and others, as non-voting consultants.

March of Dimes

Jennifer Howse, Ph.D., President of the March of Dimes (MOD), then offered a summary of the March of Dimes' recent activities. Dr. Howse emphasized the March of Dimes' focus on the needs of the newborn and the need for greater uniformity in testing. MOD identified the irreducible minimum of newborn screening tests that they would recommend, called “core tests.” Using two criteria—that the test be reliable and that the condition identified be treatable (meaning that early discovery of the condition would make a demonstrable difference in the health of the newborn and the child)—they arrived at a list of nine core tests, plus newborn hearing screening. Dr. Howse said that “we believe that a test, even for a rare disease, as long as its early discovery makes a difference to the child, must be conducted for every newborn”—a

sentiment that also was published in the August 2000 issue of *Pediatrics*, stimulating national debate.

At the time of that inventory in the year 2000, nine States performed all 10 tests. Using advocacy to persuade other States to adopt these tests, the March of Dimes persuaded 25 States to perform the core tests. MOD recommends that the Committee propose a set of core newborn screening tests with whatever criteria this group deems appropriate, so that regardless of what State a child is born in, he or she is guaranteed a minimum set of tests. MOD also supports when States add tests, beyond the 10 March of Dimes recommended core tests.

Dr. Howse stated that it is essential to be prepared and to have a strong foundation on a state-by-state basis, so as this field grows and matures, and the science comes to bear on so many different tests and conditions, we will be in a position to reap the benefits of that progress for our newborns.

Committee members then discussed the meaning of “genetic test” and the fact that many people don't view newborn screening as genetic testing, when in reality, newborn screening is by far the most common type of genetic testing done in this country. Committee members also discussed the difference between the types of technology necessary to conduct various types of genetic analyses. It was noted that one State screens for toxoplasmosis as part of newborn screening, which is not a genetic test; thus, it may not be under the purview of this Committee.

American Academy of Pediatrics

E. Stephen Edwards, M.D., began by urging Committee members to remember that first and foremost they are dealing with children and families, not just diseases. The mission of the American Academy of Pediatrics and its 57,000 members is to obtain optimal physical, mental, social health and well-being for all infants, children, adolescents, and young adults.

Dr. Edwards highlighted the Academy's initiatives around heritable disorders and genetic diseases. The Committee on Genetics, which consists of 6-8 experts in the field appointed by the Board, studies and makes recommendations to the Board of Directors on recent advances in

genetics. It also provides support to chapters on state legislative issues as they relate to genetics, primarily through the development of policy statements, clinical reports, and technical reports. Current policy statements have been developed related to health supervision guidelines for children with Down's syndrome and other genetic disorders; folic acid for the prevention of neural tube defects; maternal phenylketonuria; and newborn screening fact sheets. A number of statements are also in development, covering the topics of prenatal screening and diagnosis for pediatricians, molecular genetic testing in pediatric practice, and newborn screening for congenital hypothyroidism, among others.

The Academy's Section on Genetics and Birth Defects, which has approximately 250 members, is the Academy's home for AAP Fellows who are interested in pediatric genetics. The Section's principal activities are related to education, including the development of articles and educational programming; advocacy, especially related to appropriate reimbursement; program development; and young investigator recognition.

The Academy's Division of Children with Special Needs works on a number of HRSA- and CDC-funded activities. MCHB-funded activities include the Newborn Screening Task Force Report entitled "Serving the Family from Birth to the Medical Home," other initiatives related to newborn screening for sickle cell disease, and early hearing detection and intervention. Activities funded through the CDC include activities related to developmental screening for the early identification of autism spectrum disorders and the *PediaLink* Module, an online CME course addressing childhood hearing screening, which discusses genetic causes of hearing loss.

Dr. Edwards then briefly discussed the concept of the medical home. He described it as an approach to providing health care services in a high-quality, comprehensive, and cost-effective manner. The provision of care is accomplished through a primary care physician, or other appropriate physician, working in partnership with other allied health care professionals and the family. The medical home is accessible, family-centered, continuous, coordinated, comprehensive, compassionate, and culturally effective. Dr. Edwards concluded by noting that in addition to considering the science behind testing, the Committee must also keep in mind the system of care.

Secretary's Advisory Committee on Infant Mortality

On behalf of James Collins, M.D., Chair of the Secretary's Advisory Committee on Infant Mortality who was unable to attend, Dr. van Dyck commented on the Committee's activities. The Secretary's Advisory Committee on Infant Mortality (SACIM) was formed about ten years ago and is comprised of 20 members with expertise in infant mortality, representing the broad interests of academia, insurance, the private and public sector, nurses, and social workers. The purpose of the Committee is to advise the Secretary on two issues—issues that surround infant mortality and how the Department can better decrease infant mortality in the United States, and issues related to the Healthy Start Program. The Healthy Start Program is a federally funded program with the goal of reducing infant mortality that provides grants to approximately 100 communities throughout the United States that have the highest rates of infant mortality, particularly among minority infants.

The Committee has issued three reports in the last two years. The first report analyzed the increasing incidence of low birthweight across the United States. Conclusions from this report supported recommendations to the Secretary on what might be done within the Department to begin to reverse this trend. SACIM recommended that there be an integrated, coordinated approach across all agencies within the Department on research related to low birthweight, and recommended to the Secretary that an interagency coordinating council be formed in the Department to address low birthweight. This Committee was formed about nine months ago and is chaired by Duane Alexander, the Director of NICHD, and Dr. van Dyck. They will be issuing a report within the next several months detailing all research in the Department related to low birthweight, the research direction of each agency over the next five years, and how coordination efforts might be improved. A second report issued by SACIM addressed Healthy Start and ways to improve coordination, collaboration, and evaluation of Healthy Start sites. The third report addressed early discharge of new mothers from the hospital. A Committee was assigned by congressional legislation to examine whether early discharge was helpful, harmful, or neutral, and to issue recommendations.

The Committee membership will soon be changing, and they will be looking to address new issues. Issues currently “on the table” include antecedents of low birthweight; the increasing

incidence obesity, particularly in pregnancy; prenatal care issues; international comparisons of infant mortality; long-term outcomes of low birthweight; fertility and low birthweight; the effect of decreasing state budgets on infant mortality and service delivery; the standardization of data collection across states related to low birthweight, including the timing of birth/death matching; injuries in the first year of life, and contribution of injuries to infant mortality and morbidity; sudden infant death syndrome; the Back to Sleep campaign; and the contribution of newborn screening to infant mortality and morbidity in infant mortality in the first year of life.

Dr. van Dyck concluded by noting that there is potential for synergism in the recommendations coming from this Committee and the SACIM.

Secretary's Advisory Committee on Genetics, Health, and Society

Reed Tuckson, M.D., Senior Vice President of Consumer Health and Medical Care Advancement at UnitedHealth Group, presented an update on the activities of the Secretary's Advisory on Genetics, Health, and Society (SACGHS). SACGHS's mandate is to explore, analyze, and deliberate on the broad range of human health and societal issues raised by the development and use, as well as potential misuse, of genetic technologies and make recommendations to the Secretary. The scope of the mandate includes assessing the integration of genetic technologies into health care and public health; studying the clinical, ethical, legal, and societal implications of new medical applications and emerging technological approaches to clinical testing; identifying opportunities and gaps in research and data collection efforts; exploring the use of genetics in bioterrorism; examining the impact of patent policy and licensing practices on access to genetic technologies; analyzing uses of genetic information in education, employment, insurance, and law; and serving as a public forum for the discussion of emerging scientific, ethical, legal, and social issues raised by genetic technologies.

The Committee's membership represents a broad range of expertise. During the initial meeting in June 2003, the members reviewed several topics, including the current status of genetic technologies and their current uses; emerging developments and research directions; health care financing of genetic technologies; current issues related to patent and licensing practices; and current understanding of the ethical, legal, and social implications of genetic technologies. Two

action items resulted from the meeting: a draft of a letter to the Secretary supporting the legal protections against genetic discrimination in health insurance and employment and a request for information from Federal agencies and the private sector on activities addressing the education and training of the workforce in genetic issues.

Subsequent meetings addressed the issues of oversight of genetic tests and laboratories; the role of pharmacogenomics, genetics education, training, and workforce issues; how other industrialized countries approach these issues; and genetic discrimination legislation. As a result of these meetings, an inter-meeting task force was appointed to begin a systematic prioritization of all of the various issues that had been brought before the Committee.

SACGHS then classified several issues they had discussed as high priority, including coverage and reimbursement of genetic technologies and services, large population studies, pharmacogenomics, and direct-to-consumer marketing of genetic tests. The Committee is preparing a report and recommendations on coverage and reimbursement of genetic technologies and services. It also has prepared a resolution on direct-to-consumer marketing. Those items the Committee decided required short-term action and monitoring were genetic discrimination, education and work force training, and a vision statement. Consequently, the Committee sent another letter the Secretary, pressing the need for introduction and passage of S 1053 in the House of Representatives. The Committee also is preparing a resolution on the issue of genetic education and training of the work force.

Dr. Tuckson concluded by stating that SACGHS looks forward to working with this Committee in the future.

National Institutes of Health

Dr. Duane Alexander, M.D., Director of the National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH) spoke about genetic testing and screening from NIH's perspective. NIH's role in newborn screening began with the evaluation of screening for PKU—to document its usefulness in reducing the likelihood of mental retardation occurring if the intervention was carried out properly in response to the

diagnosis in the newborn period. That evaluation demonstrated that affected children, when they were screened appropriately and treated early, had IQs that were not significantly different from those of their unaffected siblings. With that assurance, the program went on to expand to all 50 States and now prevents about 250 cases of mental retardation due to PKU each year.

NICHD had a role in the development of other tests that are used in newborn screening. The methodology for screening for congenital hypothyroidism was developed in an NICHD-supported laboratory by Dr. Delbert Fisher at the University of California. His microassay for T4 and TSH, from the same newborn filter paper blood spot as used for PKU screening, made possible this particular addition to newborn screening, with similar effectiveness. This test prevents about 1,000 cases of mental retardation from congenital hypothyroidism a year and is the other test that is done in all States.

The NIH also has been engaged in other activities, particularly gene discovery, supported by their research, which is an essential aid to screening and testing. One example is cystic fibrosis, for which a study evaluates the effectiveness of newborn screening and early treatment and intervention for this condition.

Another program at the NIH that is of interest to this Committee is the Ethical, Legal and Social Issues (ESLI) program in the National Human Genome Research Institute. By law, Congress provided a set-aside of 3 percent of the budget of the Genome Institute for these types of studies, and there are a number of studies that have been done or are ongoing that relate to genetic testing and screening, including newborns.

Another study that is being supported by the National Institute of Diabetes, Digestive and Kidney Disease is of some interest. Although a specific gene for Type 1 diabetes has not been identified, nor is it a single-gene disorder, screening tests have been developed that indicate an increased likelihood of developing Type 1 diabetes. The State of Washington, with support from NIDDK, has instituted a program using these tests to identify people at higher risk for developing Type 1 diabetes, and then following them and investigating whether the development of the condition, as well as knowledge that they are at a higher risk for developing it, makes it possible to detect or intervene at an earlier point in time. To date, the results suggest that people

identified as being at high risk are more likely to be identified as having Type 1 diabetes before they present with ketoacidosis than if they were not.

Dr. Alexander then discussed the National Children's Study. This is a national longitudinal birth cohort study of environmental influences on children's health and development. The Congress mandated that this study be conducted as part of the Children's Health Act of 2000. The lead agencies are NICHD, the National Institute of Environmental Health Sciences at NIH, CDC, and the Environmental Protection Agency, which formed the Interagency Coordinating Committee that is leading the planning for this study.

The concept of this study is to include the children of approximately 100,000 women and their families identified before or during pregnancy and follow them until they are 21 years of age, collecting information on environmental exposures from parents, DNA from both parents and the child, following the course of the pregnancy, labor, and delivery with observations of the child in the newborn period, the first year of life, again at age 2, and then at intervals after that time. The study would involve sampling the environment, as well as specific measures of toxin levels in the parents and child. Investigators will look for gene-environment interactions, but also will look at the environment from a much broader perspective than just the physical and chemical environment of the child, including the social, behavioral, and cultural environment.

Dr. Alexander noted that the size of the cohort and the large number of variables studied will allow for the establishment of cause and effect relationships, and the investigation of the interaction of a variety of variables with each other. More than 40 departments and agencies are involved in this study, as well as hundreds of scientists.

If the necessary funding is obtained, the pilot of the study protocol will be conducted in 2005, with recruitment of the actual subjects for the study by the end of 2006, but funding is not yet in place. The total cost of this study over 25 years is about \$2.5 billion, averaging \$100 million a year.

Another NIH activity related to newborn screening, funded under a grant to the University of North Carolina, is a study on screening for Fragile X syndrome. The study will screen about 1

million newborns for Fragile X syndrome in selected States, and the data collected will answer a number of research questions, including

- The incidence of Fragile X
- Whether it varies as a function of ethnicity
- How acceptable screening for Fragile X syndrome is to the public
- What proportion of parents will voluntarily participate in screening and what characteristics differentiate patients who choose not to participate
- What are the relative effectiveness and acceptability of different models of informing families about Fragile X status, and supporting them in gaining information about the disorder and their reproductive risk?
- Does the bonding and attachment relationship between parents of children with Fragile X syndrome differ from that of parents of normally developing children or children with non-heritable disorders?
- How does knowledge of reproductive risk affect subsequent reproductive decisions of parents of children with Fragile X?
- What patterns of development characterize infants and toddlers with Fragile X syndrome and how do these patterns vary as a function of factors such as Fragile X mental retardation protein, physiologic variables, SES, gender, and autism?
- What is the efficacy of contrasting models of early intervention for children with Fragile X and their families and does treatment efficacy vary in accordance with severity and nature of disability; and what patterns of coping and adaptation characterize families of children with Fragile X syndrome during the early years?

Dr. Alexander noted that there is not currently a therapeutic intervention directed specifically to the Fragile X mental retardation protein that is effective.

Dr. Alexander then addressed the issue of microchip-array screening, which allows for the screening of many conditions at once. However, he noted that to do this many of the disorders screened for will not yet have effective treatments, which may require changing the “standard dogma” of screening only for disorders for which there is treatment or, alternatively, broadening the definition of what constitutes treatment to include developmental interventions, presymptomatic treatment interventions, avoiding patients having to “shop around” for a

diagnosis once symptoms become apparent, and family planning benefits. Dr. Alexander suggested as part of this expanded screening the establishment of a registry, with parents' approval, of potential study participants. Dr. Alexander noted that the physician community, as well as parents, must be prepared to address issues such as informed consent. Dr. Alexander closed by emphasizing the importance of developing early interventions for disorders identified through screening, and noted that NICHD is preparing a program announcement to this effect.

Committee members then discussed how they might be supportive of a study such as the proposed National Children's Study, so as to avoid competing initiatives at a fragile budget time. They noted that this is important given that large population studies will be going forward.

Health Resources and Services Administration

Peter van Dyck, M.D., M.P.H., Associate Administrator of the Maternal and Child Health Bureau at HRSA, shared some of the programs HRSA has funded related to this Committee's charge. The mission of HRSA's work is to assure high-quality health care to underserved families and individuals nationwide, with the goal of moving towards 100-percent access to health care and zero health disparities for all Americans. As a service agency, HRSA's vision is to assure the availability of health care to low income, uninsured, isolated, vulnerable, and special needs populations, and to meet their unique healthcare needs. Out of the bureaus and offices in HRSA, the primary genetic and newborn screening activities occur in MCHB and the Bureau of Health Professions (BHP).

HRSA's programs, in partnership with NIH, AHRQ, CDC, and with States, private organizations, public organizations, and universities, are established to facilitate an increase in health professionals' genetic knowledge, and the improvement their ability to practice scientifically appropriate medicine now and in the future. BHP increases health care access by assuring a health professions workforce that meets the needs of the public. BHP projects conduct faculty development, curriculum development, continuing education, and graduate and undergraduate education. They develop the health professions workforce through research, analysis and planning, improve distribution and diversity of health professions, particularly in rural or urban underserved areas, improve the quality of health professions practice and

education, and focus on key 21st Century health professions issues such as geriatrics, genetic translation, and diversity and distribution. MCHB and BHPPr have funded a number of projects, including the American Academy of Family Practice's clinical focus in 2005 in genomics (MCHB); Genetics Through the Primary Care Lens at the University of Washington (MCHB); Genetics in Primary Care: A Society for Teachers of Family Medicine (collaborative project between HRSA, AHRQ and NIH); faculty development for nurse practitioners, physicians assistants and certified nurse midwives; predoctoral and residency training in primary care; Genomics Education for Advanced Practice RNs; genetics education program for RN faculty at the University of Cincinnati, and the Genomics Revolution in Public Health, an effort between the American Association of Public Health and HRSA.

MCHB's mission is to provide national leadership to strengthen the MCH infrastructure, to assure the availability and use of medical homes, and build the knowledge and human resources necessary to assure continued improvement in the health, safety, and well being of the MCH population. Dr. van Dyck noted that the MCH population includes all America's mothers, infants, children, adolescents, and their families. It includes individuals across the lifespan, women of reproductive age, fathers, and children with special health care needs.

The mission of the Genetics Services Program is to improve: early identification of those with or at risk of developing heritable disorders; the development of genetic services that are comprehensive, accessible, family centered, and culturally competent; and the understanding of the genetic contribution to health and disease upon which services are based. Program goals include

- The facilitation of the development of public health and health care infrastructure to enhance and expand newborn screening programs
- To improve linkages among them and the State and community systems of care for children and youth with special health care needs
- To examine emerging issues and evaluate emerging technologies in genetics, with a special emphasis on financial, ethical, legal and social implications
- To improve the genetic literacy of the MCH population by enhancing its understanding of the benefits, risks, limitations, and implications of genetic testing

- To provide leadership in defining the educational needs in genetics of health professionals working with the MCH population
- To support the hemophilia diagnostic and treatment centers, and thalassemia and sickle cell disease programs as models of comprehensive care for the delivery of genetic services, which include testing, counseling, education and coordinated systems of services
- To build on the expertise gained from the genetics activities to provide national leadership on expanding and enhancing genetic services for the entire population.

A few programs supported by the Genetic Services Branch include public education grants with MOD and the Genetic Alliance; a program on developing a family history tool; and a Bright Futures for Women project to improve access to care for women across the lifespan. Training programs include general primary care programs aimed at training pediatricians, family practice and internists in genetic information; “GENE Tools” a pilot curriculum for family practice and pediatricians; and newborn screening education tools aimed at parents.

MCHB’s vision for newborn screening is a systems approach with defined public health roles at both the state and national level, which includes quality assurance; public/private partnerships for assurance of a systems approach and comprehensive, efficient care and management; and equity for families, in access to testing and follow-up, both financially and in service delivery. Program goals in newborn screening are to support a framework for effective partnerships between parents and professionals and among professions, agencies, and officials at all levels of government and the private sector; to strengthen existing public health infrastructure and to facilitate integration with the health care delivery system; to provide ongoing leadership and support for the development of newborn screening standards, guidelines and policies.

MCHB has funded a resource center, the National Newborn Screening and Genetics Resource Center, directed by Brad Therrell. It serves as a focal point for national newborn screening and genetics activities and provides related resources to benefit consumers, health professionals, the public health community, and government officials.

Current activities related to newborn and genetic services include a contract with the American College of Medical Genetics, to convene an expert panel to review the available information on

newborn screening based upon accumulation and analysis of best scientific evidence. The purpose of this expert panel is to address model policies and procedures and minimum standards for State newborn screening programs, to create a model decision matrix for changing newborn screening panels, and to develop a uniform panel of conditions for screening that might be recommended for potential adoption for State programs.

Other projects include an analysis of State statutes, regulations, and policies regarding consent for newborn screening and storage and use of residual blood spots, including recommendations for a State resource toolkit, which is taking place at UCLA and involves five States—New York, Utah, Louisiana, Texas, and Maryland. This program also will develop a sample newborn screening educational toolkit to analyze the content and suitability of one set of prime educational materials from 50 States and will prepare a draft content for educational programs for parents on newborn screening. To develop educational materials for prenatal providers to educate parents, MCHB partnered with the American Academy of Family Practice and American College of Obstetrics and Gynecologists to target health professionals with a primary responsibility for prenatal health care and for labor and delivery. MCHB also supports regional genetic services and newborn screening collaboratives to enhance and support the genetics newborn screening capacity of States within seven defined regions, undertaking a regional approach towards addressing the maldistribution of genetic and newborn screening resources.

Applicants for this grant must be willing to serve as a regional center, to promote a collaborative and regional approach towards facilitating access to the genetics expertise, services, and technology needed to diagnose and manage, and develop the infrastructure of public/private regional collaborative partnerships to provide genetic newborn screening and other relevant subspecialty services.

MCHB also supports, in partnership with the Library of Congress, the Genetic Alliance, and the American Society of Human Genetics, a consumer-based family history tool to increase the public's awareness of genetics and the analysis of models of genetic service delivery, including economic and policy issues; agenda setting to address the translation of genetic research into practice, in cooperation with Washington State.

MCHB also conducts establish two new newborn screening projects—one to establish a quality assessment and evaluation scheme for newborn screening programs at the National Newborn Screening and Genetic Resource Center and another to support a newborn screening informatics practice network to develop best practices for newborn screening integration projects.

After Dr. van Dyck's presentation, members asked about the funding given to Title XXVI. Dr. van Dyck stated that Title XXVI has no funding at this point for carrying out other activities to help develop a system of newborn screening and to help States get equity and that the Committee should take that into account when developing recommendations.

Standardization of Guidelines and Practices for Newborn Screening Programs

Michael Watson, Executive Director of the American College of Medical Genetics (ACMG), presented the Committee with an update on ACMG's MCHB contract to study the standardization of outcomes and guidelines for State newborn screening programs. Noting the great variation in the number of mandatory disorders screened for in the United States, Dr. Watson explained that the primary goals of the HRSA/ACMG contract are to develop a uniform panel of newborn screening conditions and to develop a decision-making tool for use in newborn screening program expansion or contraction, using criteria for assessing conditions for their appropriateness for newborn screening. The secondary goals of the contract are to enable program evaluation to ensure realization of expected outcomes, including the development of minimum standards and related policies and procedures for newborn screening programs; the identification of appropriate health outcomes to be incorporated into evaluation protocols; and a consideration of the value of a national process for quality assurance and oversight of newborn screening.

Dr. Watson gave a brief overview of the process used to achieve these goals. A steering Committee was formed that included a number of major organizations with interest and involvement in newborn screening, such as the AAP, the March of Dimes, the Genetic Alliance, HRSA, and CDC. An expert group representing the full spectrum of interest groups in newborn screening also was formed, chaired by Dr. Howell. The next stage of the process was to gather input about potential issues to consider, from invited speakers from various areas of medicine

and interest groups, both from the United States and from international groups, as well as from the public.

After a literature review, workgroups were formed within the group to address a uniform panel and criteria, diagnosis and follow-up systems, and an external review group that commented on early drafts of materials. They are now in the process of finalizing their recommendations.

Dr. Watson stated that the project's overall strategy in beginning this project was to look at the issues very broadly and to be as inclusive as possible. The initial list of potential disorders included endocrine disorders, infectious diseases, hemoglobinopathies, genetic conditions, inborn errors of metabolism that could be detected by tandem mass spectrometry, other inborn errors that may or may not be detectable by tandem mass spectrometry, a number of lysosomal storage diseases, and other conditions as well, for a total of 83 conditions plus other "add-ins" that were suggested.

The first stage of the process was to develop overarching principles to help draw lines in data and in literature information around priorities that the group developed. Members thought that universal newborn screening was an essential public health responsibility, critical to improving the health outcome of affected children and that newborn screening policy development should be driven primarily by what is in the best interest of the affected newborn, with consideration of the interest of unaffected newborns, families, health professionals, and the public. In addition, newborn screening is more than just a test. It is a coordinated, comprehensive system that includes education, screening, follow up, diagnosis, management, and program evaluation. All of those things have to be put into place for newborn screening to work effectively.

The group also felt that the medical home and the public and private components of the screening program should be in close communication to ensure confirmation and the appropriate follow-up care for the individuals who are identified and that the recommendation of conditions appropriate for newborn screening should be based on an evaluation of the scientific evidence and expert opinion, both now and in the future. To be included in a newborn screening program, the Committee decided that the condition should meet several criteria—be identifiable at a phase at which it would not ordinarily be recognized clinically; have an available test with appropriate

sensitivity and specificity; and that there are demonstrated benefits of early detection, timely intervention, and efficacious treatment. The seventh principle was that the primary targets of newborn screening should be conditions that meet the criteria previously mentioned. The newborn screening program also should report any other clinically significant result. The Committee felt that there should be centralized data collection for longitudinal assessment of disease-specific screening programs; that total quality management should be applied to newborn screening programs; that newborn screening specimens are valuable health resources; and that public awareness coupled with professional and public education and training are significant program responsibilities that have to be part of the newborn screening system.

Dr. Watson then highlighted the criteria that the group developed. The criteria are: incidence of condition; whether signs and symptoms are clinically identifiable in the first 48 hours of life (higher weight would be given to disorders that are not readily clinically identifiable); burden of disease; whether there is a sensitive and specific screening test currently available (test characteristics also were considered); availability of a treatment; cost of treatment; potential efficacy of existing treatments; benefits of early intervention to the individual; benefits of early intervention to family and society; whether early diagnosis and treatment prevents mortality; availability of diagnostic confirmation; availability of providers for acute management of the condition; and finally, the simplicity of the therapy.

Two hundred and eighty people responded to the development of these criteria, for a total of 3,932 conditions scored. Dr. Watson noted that participants often had varying opinions on the importance of different criteria. A wide array of people responded—people involved in testing, the follow-up system, administrative and newborn screening programs, policy development, primary care providers, consumers, and specialty care providers. It was important to obtain a respondent group balanced with regard to geography, population size, constituency, and expertise.

Responders were not always able to comment on each of the criteria for each disorder listed. Therefore, in order to pool results, the expert group examined the sum of the mean scores for each criterion, rather than individual scores for a particular disorder. The report will identify the gaps in knowledge for each disease so that it will be easy to see how each disease was rated.

Expert group members used the scored criteria, the literature review, and expert opinion to evaluate the conditions. Independent surveys were conducted to assess whether criteria were being properly weighted. The next stage of decision making involved consideration of new tests and technologies that are driving the system, including multiplex capability, and tandem mass spectrometry. Finally, the expert group then focused on ranking disorders and providing a cut-off point for a uniform panel. They developed two groups of conditions, those considered to meet all of the important criteria, termed the “core screening panel,” and then a set of conditions that may not be treatable but are going to be identified in a multiplex test, termed the “report only” conditions, for which a doctor may choose to follow patients, collect data about them, and make decisions. Thirty conditions were chosen for the core panel category and 22 more conditions in this report- only category. The conditions that scored highly, for which there was a treatment in place, and of which there was sufficient knowledge of natural history were included in the core panel category.

The group also considered whether the infrastructure exists to make sure that a recommendation that included 30 core conditions was feasible. Several key components of these programs are necessary, including education, screening, follow up, diagnosis, disease management, and program evaluation. The final report will include discussion on what each State does for each of these important components.

The expert group still has more work to do. Data is still being reviewed for several conditions, including cystic fibrosis, hearing loss, and G6PD deficiency, and infectious diseases have not been reviewed. The group also is working on validating the utility of tools that can be used by States to evaluate disorders for inclusion in their newborn screening panel. A number of state programs have begun to look at how to use this tool and have integrated it into pilot testing.

Other issues that arose throughout the course of the group’s analyses included the development of a research agenda based on gaps in data analysis, the identification of conditions amenable to infant screening, standards for hospital-based screening, cost effective analyses, and issues related to how the newborn screening field is evolving (state-mandated vs. standard of medical care). Another important issue is the use of a collaborative management model; the group has

begun to look at developing confirmatory algorithms and guidelines for the individual diseases and their confirmation and management.

Dr. Watson concluded by mentioning several issues to be addressed in the future. These include screening after the neonatal period, lysosomal disorder tests and treatments that will soon be available, hyperbilirubinemia practice monitoring, and disorders of mental disability.

Following Dr. Watson's presentation, the Committee discussed the variety of issues highlighted over the course of the meeting. They discussed the quandary of how to develop an evidence base for conditions that are extremely rare and whether expert opinion is appropriate when developing public health mandates. Members agreed that they could accumulate evidence, clearly, by developing data collection systems on people identified. Dr. Watson noted that data can be collected on these types of diseases as they are identified, and noted that even in the case of cystic fibrosis, the large numbers of gene mutations that cause the disease are very rare, yet data has been collected through the development of new technologies. He noted also that there are a lot of programs being established to collect evidence around rare diseases, especially through the Office of Rare Diseases at the NIH. Committee members observed that one of the challenges for newborn screening programs is the insistence on having scientific or evidence-based information backing them up. What do we do when we don't have that good evidence-based foundation to stand upon?

Committee members then discussed what power these recommendations from the ACMG have as far as the States are concerned, especially with regard to financing. Dr. Watson explained that the recommendations will go to HRSA, and this Committee will help in making decisions regarding the recommendations outlined. Dr. Watson hopes the report will help States think about their newborn screening panels in the short-term, while this Committee considers how to bring uniformity to the system. Dr. van Dyck explained that it will ultimately lead to a recommendation of a core panel of tests coming from MCHB "but it's not something that's going to be done lightly and without thinking about the whole system."

It was then suggested that since the ACMG report may serve as a basis for the Committee's deliberations on the issue of newborn screening, that the Committee set aside time at the next

meeting to devote to the report and to delve deeper into all its nuances and implications, including a detailed discussion of the evidence, the capacity of the current system in terms of technology, follow up, and education (including regionalization, and State and national boundaries), the cost effectiveness of potential recommendations (especially given State budgetary concerns), and how to connect the Committee's recommendations with the distribution of potential Title XXVI funds. Committee members were asked to remember the practical considerations in States trying to implement core standards, including the possible necessity of changing State laws and regulations—Alissa Johnson, a representative from the National Conference of State Legislatures offered assistance in developing a set of questions States might need to address before they move forward with the implementation a core panel of tests.

Public Comments

Public comments were received from various individuals representing industry, family advocacy organizations, parents, community-based organizations, and research groups.

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Thank you for this opportunity and for your work on behalf of children and families with inborn errors of metabolism.

I am president and CEO of a start-up company, LysoPlex LLC, which is dedicated to developing technology discovered by Professor John Hopwood for screening newborns for lysosomal storage diseases. I come to the newborn-screening world from the perspective of the

pharmaceutical and biotechnology industry where I have been involved with development of enzyme replacement and gene therapies for patients with lysosomal-storage diseases.

As you know, lysosomal-storage diseases or LSDs are a group of approximately 50 inborn errors of metabolism resulting from mutations in enzymes comprising the normal degradation pathway of cellular biomaterials. As a group, LSDs are among the most frequently observed genetic diseases with a combined incidence of 1 in 5,000. Put into perspective, the group of LSDs has an incidence approximately half that of cystic fibrosis but several times larger than many diseases currently screened.

The key difference with LSDs versus the classically screened diseases is that simple measures such as changes in diet, prophylactic penicillin or avoidance of fasting cannot improve the patient's outcome. Therapeutic action must be taken, and in many cases, be taken rapidly—before severe damage has taken place. Children with LSDs often experience severe mental retardation in many diseases or organ failure in others. The action needed involves replacement of the deficient enzyme through bone marrow transplant or exogenous replacement of the missing enzyme—enzyme replacement therapy. The Food and Drug Administration has recently approved a third approach: substrate inhibition therapy which helps in certain diseases. These measures are not inexpensive, nor in the case of bone marrow transplant, innocuous. In spite of their drawbacks, however, these therapies are the only option for these children and their families. In time, it is my hope that gene therapy or other curative technologies will be developed to definitively treat these children once they are diagnosed.

In every case, determining that the child has treatable LSD is the trigger that enables initiation of therapy. If treatment is sought after the beginning of symptoms, it may be too late. In some cases therapy must be initiated within days or weeks following the diagnosis whereas in other situations, it may be satisfactory to carefully watch the patient and initiate therapy at the first subtle signs of the diseases—well before critical organ function has been lost. Regardless of when therapy is initiated, we believe that providing the diagnosis to the parents can enable them to plan for the future; not only in establishing the prognosis of their current child but also in planning for future pregnancies. One of the tragedies we hope to avoid is the subsequent birth of affected children while the parents are still trying to gain a diagnosis for the first child. This happens all too frequently.

So, what requests does LysoPlex have of this committee and the Federal Government?

Continued advocacy for universal access to newborn screening

We acknowledge that States have primacy in the conduct of newborn screening. However, all children born in the United States should be protected through universal and equal access to testing—regardless of where the child is born. The current system is complex and unwieldy, particularly when it comes to payment for newborn screening. The marked variability of diseases tested among the States is a disappointment. Concentration of expertise in regional centers with substantial Federal support could be a route to universal testing.

Continued support for development of new technology which enables testing for inborn errors of metabolism beyond the current group of screened diseases

LysoPlex is taking forward a novel multiplex technology which enables simultaneous measurement of multiple lysosomal proteins. As small, flat organizations, biotechnology companies often can translate discoveries into approved products faster than other organizations—especially when combined with ready access to the knowledge and resources of the Federal government. The ability to rapidly mobilize these Federal resources could be extremely beneficial to start-ups that must often bootstrap themselves from a very modest base prior to professional investment.

Continued leadership role in the establishment of national recommendations which will encourage States to rapidly incorporate these new technologies into state screening procedures

The work conducted by this committee in defining what diseases should be screened for is crucial. In addition we propose that the Federal Government also provide the financial backing and incentives for states to broadly incorporate these national recommendations into their standard newborn screening procedures.

Once again, thank you for your time and your service to these children.

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Chairman and Members of the Committee:

My name is Wendy Berry West, Executive Director of the Ohio Sickle Cell and Health Association and member of the Sickle Cell Disease Association of America, Inc.

First of all, I would like to thank you for the opportunity to testify before you today regarding Newborn Screening as it relates to the devastating illness of Sickle Cell Disease.

As you may know, Sickle Cell Disease affects more than 70,000 Americans. Each year 2,000 children are diagnosed with the disease. One in 400 African Americans are affected by the disease and 1 in 10 have the trait (carriers) of the disease. Sickle Cell Disease is a genetic condition that does not only affect African Americans, but persons of Hispanic, Asian, Indian, Greek, and Mediterranean descent. Its devastating affects on the individual as well as the family are long term.

There are three areas that I hope that the Advisory Committee considers as it makes its recommendations to HHS Secretary Tommy Thompson. The three areas of concern for Newborn Screening should relate to expansion, standardization, and funding.

Expansion

NBS should be an expansion of existing services, that are culturally appropriate, and comprehensive and that provide opportunities for universal health care that will encompass the ideology of Medical Homes for newborns and childrens affected and at risk for SCD.

Standardization

Counseling, education, and testing protocols should be standardized to provide the most effective and enhanced services for the targeted population. This will assist health professionals to provide care that is sensitive, accessible, and appropriate for the disease.

Funding

Appropriations to support services and improve screening should ensure and supersede existing funding levels:

- So that the state-of-the-art testing is available universally,
- To allow for assistance to programs that provide direct and indirect comprehensive and competent services to individuals and families effected and at risk,
- To ensure that in this country we are as advanced as other countries that provide Newborn Screening, as well as to allow for room for advancement.

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My name is Jill Fisch. I live in Scarsdale, New York with my three children Zach (12), Sara (8) and Matthew (3 1/2), and my husband Peter. I am the New York State Monitor for Save Babies Through Screening. I also am a parent representative on the Newborn Screening Task Force and the President of Matthew's Mission. I also have recently started working with Hunter's Hope regarding Newborn Screening issues. My son Matthew suffers from Short-Chain Acyl-CoA Dehydrogenase Deficiency (SCAD). SCAD is a disorder in which the cellular enzyme responsible for processing short chain fatty acids is missing from the cells or working at a diminished capacity. This disorder can cause Failure To Thrive, developmental delays, hypotonia

or even death. We started Matthew's Mission to promote newborn-screening awareness as well as raise money for scad research. I became very involved with newborn-screening when I realized that after spending 2 years trying to get Matthew diagnosed, this was something that could have been screened for at birth. Matthew now has a feeding tube, significant hypotonia, and various other issues. After finding out he was carnitine deficient, he was started on Carnitor and gained a tremendous amount of weight. If we had known from birth, and he was started on the regimen he is on today, it is quite possible he could have had a different outcome. We will never know what Matthew's full potential could have been because he suffered do many setbacks while we were looking for a diagnosis. Finding out about Matthew caused us to find out that I also have scad. Matthew probably saved my life. Our rights as parents were taken away as we were not informed of supplemental testing. New York has the equipment to test for 60 disorders, but currently only screens for 11. One answer to this problem would be for the states to use resources in the private sector to provide the supplemental screening. Most parents do not realize that screening occurs or that options for more comprehensive screening are currently available through private labs. Unfortunately, we were one of those families. New Jersey will soon enact legislation mandating that parents be informed of additional tests available but not offered by their state program. This should be true of every state. Parental Notification of Supplemental Screening must be made mandatory. Babies are being born everyday and many are suffering adverse consequences from lack of screening. Comprehensive screening ensures that newborns are getting the best chance of starting a healthy life. I wish that Matthew had that chance. Congress should require states to inform parents in writing regarding outside screening through private labs. States that do not screen for all disorders should contract with an outside source to provide the comprehensive screening until the states are capable of doing the testing themselves. Mississippi screens for all disorders through a private lab with fantastic results. Don't all of our

babies deserve the same chance? We feel our rights as parents were taken away since we were never informed of supplemental screening. This is something that can be changed and is being changed in different states as we speak. We want to see every family give their baby the healthy start that it deserves. That is the goal of Matthew's Mission. Thank you for giving me the opportunity to share.

Hunter's Hope Foundation
Jim Kelly
Pro Football Hall of Fame Quarterback
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Thank you for the opportunity to testify on this very important issue, Newborn Screening. I became involved in the important concept of early detection as a result of my son Hunter having Krabbe disease. Krabbe disease is an inherited neurodegenerative lysosomal enzyme disease affecting the peripheral and central nervous system. Without early detection, children like my son Hunter suffer through the rapid progression of this disease. My son Hunter is currently on oxygen 24 hours a day, cannot move or speak, is fed through a JG-Tube, receives treatments every four hours around the clock of chest therapy with medication, CPT and the VEST, and takes multiple medications. In contrast, children born with Krabbe who receive early identification have access to effective treatment with hematopoietic stem cells using umbilical cord blood. This Cord Blood Transplant prevents neurological damage, halts or alters the disease process, reverses the manifestations of the disease in the central and peripheral nervous systems, saves lives and preserves quality of life. It is because of the need for early identification that I am now involved with improving newborn screening!

If Hunter had received early identification, he would have had access to the effective treatment of hematopoietic stem cell transplant using umbilical cord blood. Children born with Krabbe disease who are identified presymptomatically (currently only possible in case-index families) have had their lives saved, are now growing up, and are expected to live productive adult lives.

Our Foundation, the Hunter's Hope Foundation, which my wife Jill and I started in 1997 to increase awareness and accelerate the pace of research about Krabbe and related Leukodystrophies has already awarded more than \$3.8 million dollars in grants. Last weekend our 7th Annual Scientific and Family Symposium was attended by more than 30 families and a number of distinguished basic and clinical researchers. During the symposium I had the opportunity to spend time with many children born with Krabbe, including the children who have been treated presymptomatically. It is because of the dramatic difference between children like my son Hunter, who did not receive early identification and those who did, that I am speaking today. With a newborn screening test for four leukodystrophies (Li Y, Brockmann K, Turecek F, Scott CR, Gelb, MH: *Tandem mass spectrometry for the direct assay of enzymes in dried blood spots: application to newborn screening for Krabbe disease*. Clin Chem. Mar; 50(3):638-40 2004.) due to become available within the next few years I am here to share with you our commitment to ensuring that all children in all States receive all existing newborn screening tests possible.

Today, in the United States, thousands of our children are suffering and dying needlessly. I have heard appallingly large numbers, that thousands of infants in the United States, with treatable

diseases, go untreated each year and die due to inequities in the current newborn screening system.

I looked into why this is happening. And what I found out is that medical research and Tandem Mass Spectrometry (MS/MS) technology have advanced more quickly than our implementation of them. Today, there are more than 60 diseases that can be tested, using MS/MS, and other technologies, all of which are treatable. Most treatments are effective only before symptoms are present. This means children MUST be diagnosed and treated as early in life as possible.

The current Newborn Screening (NBS) system is legislated by State. The range in number of diseases tested is Alabama screening for four diseases and Hawaii 48. Twenty-nine states currently screen for 10 diseases or less. New York tests for 12 diseases. Children are suffering and dying needlessly because they are born in the wrong State. A child's chances for life should not be dependent on where he/she is born. No child should be denied the right to a healthy life. Nor should parents' rights be denied to know that their children are at risk due to these inequities from State to State newborn screening. It is impossible to fully express the devastation these illnesses bring to the entire family. There is a cost for freedom from disease, but the cost of the alternative is much, much greater. It extends far beyond our comprehension. I can't help but think that if we received a terrorist threat that thousands of our infants were going to be killed by the end of 2004, our Nation would use all the money and power we had to stop it and we would stop it! We have a worse threat right here, today, in our midst that is "silently" killing our children. It is within the very systems (NBS) that we established to help our children. Why are the state public health departments NOT USING ALL AVAILABLE RESOURCES, including

private sector resources to screen infants at birth? I DO NOT UNDERSTAND HOW THIS CAN BE IN THE BEST INTEREST OF PUBLIC HEALTH?

I know that once our legislators understand the importance of and need for immediate action on this issue, we are confident they will respond. We recommend that this Committee encourage Congress to require States to inform parents in writing of the potential for their children to receive additional newborn-screening tests that may not be required under state law. We must start by mandating that the hospitals educate parents on the availability of supplemental NBS tests. This parental notification must be meaningful and informed and require consent. We must immediately put a plan in place for adding all testable/treatable diseases to every State in the nation's mandatory NBS list.

The solution seems so simple. Screening tests, technology, and treatments are all available today. We just need to use them. We need to fix our current NBS system so that currently available resources are used to give every child the right to a healthy life.

Organic Acidemia Association
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Good afternoon ladies and gentlemen. It is an honor to be here today on behalf of the Organic Acidemia Association and the National Coalition for PKU & Allied Disorders. Most importantly though, I am here for my 6 year-old son Stephen, the youngest of three boys, and to tell you about the harsh reality of undetected inborn errors of metabolism.

You see, ironically, 3 years ago today, I was sitting in Stephen's ICU room alongside my husband, trying to determine whether or not to discontinue life support. Ten days earlier, Stephen had contracted a typical stomach virus, like most children do, and I treated it as such. However, I found him the next morning in a state that no mother should ever have to endure. He was lying in his crib, breathing incredibly fast with his eyes half-way opened with a distant gaze. He was completely unresponsive. Stephen was transported to our local hospital and then to Inova Fairfax Hospital's PICU. Stephen's tests revealed severe acidosis leading them to a diagnosis of a metabolic disorder. The initial test eliminated certain disorders, but others had to be sent out. Twenty-four hours later, Stephen was diagnosed with Isovaleric Acidemia, in which his body's enzyme to break down the amino acid Leucine, either doesn't exist or does not function properly. Leucine produces Isovaleric Acid and when those levels build up in the body, they can become toxic. Unfortunately, Stephen's diagnosis came too late. By the next day, he was slipping into a coma. While preparing for an MRI Stephen went into a grand mal seizure, followed by another one in the MRI. Within minutes of returning to his room, Stephen crashed before our eyes. After a great deal of intervention, Stephen was clinging to life on a respirator, with a central line and chest tube placed. It is a sight that remains etched in our minds today. The initial MRI indicated swelling around the brain stem. The weekend only brought reflexes from Stephen and another MRI that Monday, revealed extensive brain damage throughout Stephen's brain. That's when we were faced with the decision of discontinuing life support. As you can imagine, we were devastated with the news of losing our son. We asked "how could such a happy, healthy, energetic, child become so close to death in such a short time? While we were trying to come to terms with Stephen's condition and prognosis, we discovered that he was a walking time bomb waiting to ignite and that this whole situation could have been avoided had he benefited from

Comprehensive Newborn Screening at birth. We also linked a similar episode at 18 months to the disorder, but the doctors failed to recognize the signs and symptoms of the disorder. The physicians and hospital had acted within the standards of care for a small community hospital. Hindsight is brutal. Looking back, the signs were all there...strange odor, picky eating, and slow weight gain. "You had no way of knowing ," is what we were told. We gave Stephen a little more time and he started to show signs of progress. After 3 and a half weeks, Stephen received a gastrostomy tube and was removed from the respirator. A week later, he was transferred to the Kluge Children's Rehab Center in Charlottesville, VA. There we spent 6 long weeks where he endured daily therapy and care to get his body well again.

Since then, Stephen has made progress that was not to be expected. However, he is far from the little boy that he once was. He requires total care. He continues to be fed via gastrostomy tube, and he can not walk, talk, sit up, nor hold his head up without support. He also is legally blind. Stephen takes four anticonvulsant medications per day, yet still has 3 to 4 seizures a day. Due to his neurological state, hiccups usually result in a hospital stay, because his button causes GI bleeding. He recently had surgery called an orchiopexy, which is a surgical procedure to bring his testicles down. They had retracted this past year due to spasticity. Our days are filled with therapies and numerous doctors' appointments. I spend many phone hours trying to settle insurance disputes. His medical costs have exceeded the million-dollar mark and continue to climb. Stephen is now under the school system, where he has an IEP. This too is a new battle, to ensure proper care and services for Stephen. He has already outgrown his first wheel-chair, and we are awaiting another that will cost approximately \$5000. We would have much rather paid the \$25 to \$40 for Comprehensive Screening had we only known that it existed. Gone are Stephen's opportunities for a normal life, because our government and health system continue to

debate the cost effectiveness of Universal Newborn Screening. The Children's Health Act of 2000 had promised to help fund States expanded newborn screening, but has yet to follow through with the money. States are left to their own means and only 18 have decided that children's lives are worth the effort and cost. Stephen's fate was already determined because he was born in Virginia, where they only screen for eight disorders. Had he been born in our neighboring North Carolina, where the list includes 36 disorders, Stephen would be in a normal kindergarten class instead of occupying a special education slot. It is a travesty that Stephen is a statistic at the hands of beurocracy and lack of knowledge within the medical community. While the debate continues more babies are going to die and more children are going to share Stephen's fate, yet the equipment and knowledge to avoid this exists. The life of my Stephen and the thousands like him born each year should not be so devalued in a society where our constitutional rights are supposed to promise us equality. The incidences of these disorders are not as high as other diseases like cancer and diabetes, but they can be just as debilitating and deadly. Most important of all, the treatment for most of these disorders already exists.

A testimony to the significance of early detection of these disorders is our 20-month-old daughter, Caroline. With the knowledge we gained with Stephen, Caroline was diagnosed with the same disorder with prenatal testing. Early diagnosis enabled doctors to establish a protocol of care prior to her birth. With a restricted protein diet and medication, Caroline is doing well and developing normal. She is a typical, happy, healthy, toddler thanks to early detection.

Unlike Stephen, she will have a normal childhood and dreams. Although Stephen has suffered severe brain damage, and dreams have been lost, we know that his life has a purpose and we will see to it that it is fulfilled. Thank you for your time.

I am seeking your assistance to present a bill to Congress to mandate more extensive evaluations of especially High Risk newborns. This disgusting, negligent practice must be stopped. Doctors must not be allowed to so arrogantly play “God”, with our innocent children’s lives. They must be made accountable to someone. I can find no laws to protect our children. A simple blood test at birth would prevent much needless pain and suffering, but ultimately death.

I would appreciate an expedited reply on this matter. Thank you for your time and interest.

Pediatrix Medical Group, Inc.
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Mr. Chairman and members of the Advisory Committee (on Heritable Disorders and Genetic Diseases in Newborns and Children): My name is Phil Vaughn. I am a neonatologist, and currently serve as Vice President of Pediatrix Screening, a state-of-the art laboratory that provides the most comprehensive program for newborn screening of genetic metabolic disorders in the world.

Since its founding in 1994, Pediatrix Screening has analyzed dried blood spots from over 2 million newborns. Before I discuss the important role that Pediatrix Screening plays in helping State laboratories and health personnel provide the highest-quality newborn screening and clinical testing, I would like to take a moment to briefly describe the services provided by Pediatrix Medical Group (Pediatrix), the parent company of Pediatrix Screening, to aid the Committee’s understanding of how metabolic and genetic screening is a natural and complementary adjunct to the spectrum of newborn services we provide.

Pediatrix Medical Group

Pediatrix is the largest neonatal and perinatal physician group in the United States, with 700 physicians and 325 nurse specialists providing direct medical care in more than 200 hospitals across the country. We care for both premature and critically sick newborns, as well as women with high risk pregnancies. Last year, our physicians cared for around 3,000 newborns each day in hospitals in 30 states and Puerto Rico. In addition to neonatologists and maternal fetal-medicine specialists, other members of the Pediatrix team include pediatric intensivists, pediatric cardiologists, pediatric hospitalists, and neonatal nurse practitioners. Pediatrix screens over 225,000 newborns annually for hearing loss, and has been a national leader in developing newborn hearing screening programs across the country over the last decade.

Because Pediatrix is in the unique position of treating so many pregnant women and babies, we are a leader among private-sector companies in developing Best Practice standards, conducting clinical trials, engaging in collaborative research efforts, developing an interactive educational Web site (“Pediatrix University”), offering continuing medical education for physicians and nurses, and tracking the outcomes of more than 180,000 neonatal cases in a centralized database.

Understanding how traumatic a Neonatal Intensive Care Unit (NICU) experience can be for the families involved, we also work directly with parents and family members of critically sick newborns, providing brochures and other materials in easy to understand terminology in order to help prepare them to understand the workings of a NICU. We are a partner in the March of Dimes NICU Family Support program, actively working to ensure that parents are better

equipped to handle the additional emotional stress of having their newborn cared for in a NICU and at home.

I mention the scope of Pediatrix' overall efforts in direct clinical patient care, as well as its background in research, expertise in physician education, and leadership in hearing screening to show the level of commitment we bring to health care quality, and the professionalism and responsiveness to our patients and the community at large.

Our goal is to ensure the best start on a healthy life for our patients. We know that our efforts are directly contributing to more advanced treatments and better outcomes, which help all women and babies.

Pediatrix Screening Services

Pediatrix Screening embodies the same philosophies inherent in Pediatrix Medical Group. Our laboratory delivers the highest quality metabolic and genetic screening services in the most efficient and cost effective manner.

Pediatrix Screening is able to detect more than 50 disorders in newborns. The program uses a unique combination of biochemical, tandem mass spectrometry, and DNA based analysis. This spectrum of technologies delivers results with a high positive predictive value. Just as important as the number of disorders screened is the fact that definitive test results are made available to the physician or state health department laboratory typically in less than 48 hours. Health care providers involved in the care of newborns understand that accurate identification and early detection of many disorders can dramatically improve the long-term health of affected newborns.

For many of these babies, the timeliness and accuracy of test results is truly a matter of life or death.

In the tragic event that treatment is not available for a particular disorder, we still believe that comprehensive screening is extremely important. Not only can the data gained from screening for all known disorders help researchers study these rare occurrences with the goal of developing future treatments, but it can also provide answers for the parents and family members of a sick or dying newborn.

From 1996-2003, Pediatrix Screening conducted a metabolic autopsy survey of over 17,500 postmortem specimens. A metabolic autopsy looks for compounds that are markers of inherited disorders of metabolism associated with sudden and unexpected death. Pediatrix' Metabolic Autopsy Survey identified evidence of a genetic disorder in ~1 percent of all infant deaths, including some previously misclassified as infection, vaccine related deaths, SIDS, SUDS or Reye-like syndrome. Had comprehensive newborn screening been available in these cases, countless families may have been spared a measure of terror and guilt over these ostensibly "unexplained" deaths.

Supporting state public health efforts

Some of the Advisory Committee's key goals are to provide recommendations that will enhance the ability of state and local health agencies to provide newborn screening, as well as guide the Secretary of Health and Human Services in developing newborn screening tests, policies and technologies to reduce newborn deaths from metabolic or genetic disorders.

We would like to make the Committee aware that resources are currently available – and are being used effectively and efficiently – in the private sector that can help address the serious newborn screening problem. Pediatrix Screening currently partners with health care providers in 48 states and internationally, at hospitals in Latin America, South America, the Middle East and Asia, to provide a variety of newborn screening services. We also perform the state mandated newborn screening in Nebraska, Mississippi, Maryland, and Washington, D.C., and will soon resume mandated screening in Pennsylvania.

We believe that all newborns should have access to a metabolic and genetic screening program that provides for quality, comprehensive testing. Pediatrix Screening will continue to work in partnership with state and federal officials, healthcare professionals, and parents to promote this goal. We offer laboratory testing, educational support, and ongoing research in collaboration with existing state newborn screening programs.

We are aware that some believe newborn screening should only be conducted through a state-operated laboratory under the auspices of the state public health department. Concern has been expressed that overall quality of care, as well as needed documentation, follow up, and treatment for newborns found to have a genetic or metabolic disorder may suffer if states and hospitals are allowed to partner with a private laboratory to provide screening services. Some are also concerned that a state's public health role may be supplanted.

We respectfully, but strongly, disagree with these assertions. First, states where Pediatrix Screening performs state mandated testing, report exceptional quality indicators in their newborn screening programs. A rapid turn around of results allows for prompt clinical attention to infants

at risk, and a low “false-positive” rate avoids both emotional anguish for families and additional health care costs to unnecessarily evaluate healthy infants. We comply fully with all state reporting requirements, and tailor our services to the individual needs of our state clients.

Pediatrix Screening offers states, hospitals, and health providers the most advanced resources available for genetic metabolic screening, in a manner that works within the constructs of each state and local government administrative requirements. We do not supplant state public health efforts, but complement and serve as a partner for such efforts. As an organization, we bring to the table an exemplary track record grounded in the highest quality clinical care, coupled with the expertise needed to ensure that all babies are tested, diagnosed, and treated. Our goal is to work in partnership with all stakeholders to ensure a healthy start for our newest generation.

As well, it should be noted that a tandem mass spectrometer does not, in and of itself, guarantee a high quality comprehensive newborn screening program. The combination of experience and the use of a spectrum of technologies allow our laboratory to provide timely and accurate analysis for our clients and patients.

Parental notification and education: the cornerstone of any screening program

Today there is a disparity across state newborn screening programs in the number of disorders screened for. The number varies from 4 disorders to the state of the art 54 offered by Pediatrix Screening. One result of the current extreme disparity in the level of various state screening programs is that parents of newborns may not be informed that their baby can be tested for a comprehensive set of disorders that far exceeds what is provided by their own state health department. This is particularly disturbing, since most babies born with serious metabolic or

genetic disorders rarely show any visible sign of disease immediately after birth. And, most parents do not even realize that screening occurs, or that options for more comprehensive screening are currently available through private laboratories. Sadly, it is only after the baby suffers an adverse consequence that the parent learns that the child could have been screened – and possibly treated – for the disease or defect.

For these reasons, we encourage the Committee to recommend that states be required to inform parents in writing of the option to test their newborn for a comprehensive set of disorders that exceeds the state mandated list. Continuing advances in medical technology will routinely identify new disorders, as well as new methods of treatment. Regardless of which specific disorders this Committee may recommend as part of a universal screening package, parents should be informed that they have the option to have their child tested for other metabolic genetic disorders that may be detected through an existing supplemental newborn screening program.

In closing, on behalf of Pediatrix Screening and Pediatrix Medical Group, we very much appreciate the opportunity to address the Committee today. We look forward to having the chance to discuss these issues in the future with you, and are available to serve as a resource on metabolic screening disorders or to provide any other information that may assist you in your work.

Micki Gartzke,
Mom of LeA Marie Gartzke (1996-1998)
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Thank you ladies and gentlemen of the Committee for the opportunity to share my comments with you on this very important issue of newborn screening.

We are all here together at this time, this very special first time, to improve a process—Newborn screening—that overall we all know has not kept pace with the current needs of public health. I want you to know that I am here to help you help all children receive equitably distributed newborn screening and thus, their right to a healthy start in life.

As we all know, babies are dying unnecessarily because of lack of early identification and access to effective treatment. My daughter died because she did not receive early identification.

There is treatment for her disease, but it needs to be started within the first 60 days of life. My daughter did not get diagnosed until she was 10 months old, a full six months after we started looking for a diagnosis. Consequently, treatment was well out of the range of possibilities by then. I have a crystal clear picture of the importance of newborn screening. I know a little boy born with the same disease ten days before my daughter, he was identified at birth, my daughter at ten months. Today he is in the first grade and my daughter has been buried in her grave for five and 1/2 years. My daughter's medical bills have been calculated to be nearly a quarter million dollars in her two short years. My daughter's death is but one example of the need for universal newborn screening. This committee can greatly help many families in the United States by making recommendations to Congress about how to improve newborn screening. I need to share a few of the details our lives: my husband's, my daughter LeA's, and mine, so you can see inside of a family who has lost a child due to lack of early identification and all that that means.

Loss of love, loss of companionship, loss of hopes, loss of dreams, loss of potential . . . just to mention a few.

Having married later in life, having had a long, productive and fulfilling career, I was more than excited to transition after our marriage and become a mom, a full-time stay at home mom. It seemed like a dream come true. Having been single well into my 30's I had seen a fair share of the world, I had family and friends, fulfilling work, a bountiful amount of love. But none of that prepared me for what I would encounter after my daughter was born.

On October, 14, 1996, her predicted due date, weighing in at 7.2 lbs and 19 3/4 inches, with a mop top head full of dark hair and wide-open big dark eyes, our daughter, LeA, burst into our lives and showered us with a new type of love. Her Apgars were 8's and 9's. Right from the beginning we assured her, "Someday you'll grow into your eyes, they were so big!" She was all eyes My mom said she took after me . . . I don't know. From the minute LeA arrived she was alert, looking around taking everything in. She was calm and peaceful with the typical little voice of baby cries, cries that were easily remedied by gentle touch or nourishment. Oh, I had been warned about the possible challenges of beginning breast-feeding. But LeA, she got it right away, no problem! What we didn't know at that time was that LeA was busy taking in her environment right away, as I suspect her soul knew that her time on this earth was not to be long. The first time my best friend met LeA she said, "LeA looks like an old soul, she looks wise, her gaze is deep, and it is almost like you can already hear her thinking behind those big dark eyes." And being proud new parents we felt as if we could.

Oh, what a honeymoon we all had when we brought our baby home from the hospital. She slept, she ate, and she looked around just like a new baby is supposed to. And her first smile, well the three of us melted into one when that happened. For the first four months, we had such a delightful time with our "Baby LeA" as she was quickly becoming called. Me, a mom of advanced maternal age, boy I was right on top of everything. I noted LeA's milestones, and she hit them in the first few months right on cue. I was so proud. I can see her now sitting up in the corner of the couch, shaking a jiggly toy and laughing at the sounds that were coming out of it—and she, of course, had no idea why the sounds were being made. But they intrigued her, and she showed her pleasure with them. I can still see her sitting in her bouncy chair playing with the toys on the overhead toy bar, occasionally catching herself in the mirror and smiling at herself, almost as if flirting. I remember playing "peek-a-boo" in the mirror with the baby. We did that many times and Lea giggled so much during that game, life was wonderful. But those laughs and smiles and giggles were all soon to go away, once the crying started.

Being an on top of it kind of mom I scheduled LeA's four-month check-up when she was four months old exactly, on February 14, 1997. Our pediatrician examined her and declared that she was doing wonderfully and by the way, could he take her home for the weekend as he and his wife were really missing having little ones around. I assured him I understood his enthusiasm, as the past four months had been the most amazingly joy-filled time in my 37 years. After the doctor was done with his duties, and before I left that check-up, I pulled out my list of particulars that I wanted to ask and share with him—stuff like, when do I start with solids, how to introduce a bottle—you know the usual kind of stuff. The last item on my list turned out to be rather unusual, however, at the time I had no idea that what I had noted would have devastating consequences. I said, "So what's up with the thumbs. They used to be out," and I showed him

what I meant, "and now they are just doing this tucked in thing." Again I showed him what I was beginning to see more and more on a regular basis, although not yet on a continuous basis. I looked up from my daughter's hands only to see my beloved pediatrician's face, and before my eyes, he turned white, the color drained from his face, and in the next split second, he said to me, "that thumb thing you described is called 'cortical thumbs' and it's generally indicative of a neurological problem. We'll have to get you all over to see some specialists and find out what's going on your little beauty queen." I felt like someone had just hit my head with a hammer. The full impact of that day did not hit us right away, as LeA continued to eat, grow, smile, giggle, and hit more milestones.

Shortly thereafter, we found ourselves standing right on a fault line at the epicenter of an earthquake. Our foundations were rocked. Uncontrollable, around-the-clock, unsoothable crying started. In one day, just like that (a snap of the fingers) we went from having a virtual lovefest with our daughter, to being cast as the three central characters in a dark and grim nightmare—so unimaginable by those who have not stood in similar shoes, that any description I could give would not bear the full weight of the darkness.

From happy, smiling and laughing, LeA bee-lined straight to crying—her body rigid, stiff as board. Not able to eat and inconsolable. DEVASTATING! It was an instantaneous change, as if someone had thrown a switch. The next six months were spent in what seemed like every possible clinical specialty at the Children's Hospital Clinics. From one misdiagnosis to the next, they had us orbiting the hospital, chasing hopes that something conclusive would come up. None of the doctors were looking for a zebra in their backyard, even though it was there all the time! Reflux, colic, cerebral palsy, we heard all the "umbrella" terms.

"We're sorry Mrs. Gartzke, her MRS shows that infant myelination is within normal ranges for her age," I was told. "What is myelination? How do we know it is normal? Can I see the pictures? Can you explain it?" I asked. I was looked at and treated as a mother who was overly concerned. They tried to soothe me instead of answering my questions.

IRATE does not begin to fully capture the mood that surrounded me. The very medical professionals that my daughter's care was entrusted to were not coming up with answers as I was being held hostage watching my daughter lose weight, eat slower, choke every time she tried to eat. With a feeding rate of an ounce an hour, she was choking. I called and shared these concerns with doctors. Again I got, ". . . oh Mrs. Gartzke. Sure, we'll make an appointment to get LeA into a feeding specialist, do a swallow study for starters." I can't tell you how many times I heard, "Mrs. Gartzke, the earliest appointment we have is 6 weeks from now." And in the meantime my darling baby was starving, and crying uncontrollably.

Through trial and error, we figured out that white noise and motion helped to offset a wee bit of the crying. Let me tell you, I feel as if I did not sit down for six months. We walked with LeA, she swung in her little swing so much it burnt out a motor. But it made her happy. We drove LeA. We found a route with no stops. We could drive for an hour each direction, LeA did not cry. WE WERE EXHAUSTED. We worked so hard to soothe her that we had exhausted ourselves—and still we had no diagnosis! Finally, another MRS was ordered, still outpatient, and before I could get the results I was watching my daughter shrinking rapidly. She had been up to 17 lbs and she was down to 11.5. I felt as if I was watching her die in my arms. ENOUGH! I called the pediatrician whom I dearly loved and said, "Dear sweet doctor I have a dilemma, I

believe LeA is dying in my arms today from starvation and no one is helping her find the exact problem, and I cannot take it at home anymore with her. I am leaving in one hour for the hospital and you have two choices, either I bring her through the ER (which I don't imagine will reflect well on you) or you get her admitted ASAP and call me back. I am leaving in one hour." He called me back. We were admitted. After the 20-minute car ride to the hospital LeA had perked up again and I even have a picture of her smiling in the waiting room at the hospital. One of her last smiles!

A seven-day stay in the hospital accomplished what had been unobtainable in the previous six months. And then the long-awaited impressions from the second MRS. I could tell by the doctors' attempt to not have long faces, that the news WAS NOT GOOD! "Mrs. Gartzke," that's all I let them say before I asked, "What are the impressions this time and please don't tell me inconclusive again. This child is dying, There is something wrong." We think it is a white matter problem and most likely a Leukodystrophy, specifically, Globoid Cell. Suddenly they were speaking Greek, or I was deaf. I wasn't sure, but none of it made sense! They still did not want to deal with the possible depth of the situation, insisting that we wait til the blood tests come back with conclusive results before they would talk to me about anything.

CRAZY, this is all CRAZY, I thought! I immediately called my Internet savvy friend and had her looking for anything and everything on globoid cell leukodystrophy. And within an hour, she was in my room with information from something called PUB MED with a list of citations of research projects done on this disease, as well as a Web site about a little boy named CJ, who also had been recently diagnosed with the same disease. Three days later, at the end of the day, the neurologist came in with a plethora of followers and confirmed one of the impressions from

the MRS. LeA was deficient in an enzyme called galactocerebrosidase and this was causing her problems. By then I had learned about this disease through my own reading knowing that this enzyme was crucial to forming myelin during the vital early stages of brain development, and at best what he told me was minimal. "It's fatal, there's nothing you can do, take her home and make her comfortable. Call the ULF, they may be able to offer some parental support." Shortly thereafter he walked out of the room, his team of followers on his heels. In front of 15 strangers, in a small hospital room, the man had dropped a bomb on our family and he did not seem to find it out of the ordinary to convey such disastrous news to our family with an audience gawking at us. It felt like torture upon torture. Fatal, and your daughter, are words that should not be allowed to be used in the same sentence, especially when your daughter is smiling at you and she is ten months old. Well, that was the end of Stage Two, August 7, 1997. My birthday.

Stage Three started when we went home with an NG tube in my daughter, who was gaining weight like there was no tomorrow, she went directly from the 3-6 mos. size she had been wearing for six months to 18 month size like a week. The crying was abated by the use of nutrition and a couple of starter meds. LeA was scheduled for a feeding G-tube within weeks. A hospice nurse came to our house, the first of many, to teach us how to use the feeding pumps, tubes, suction machine, oxygen. By then we had already learned about CPT and were well ensconced in daily sessions of OT and PT. She remained stable for four months—if you can call feeding tubes, oxygen and suction machines stable? I'm not sure. New Year's Day LeA crashed. Her hospice worker came over and told us that she believed this was LeA's last day of life. Well, I tell you, after hearing, "It's fatal, there's nothing that can be done," I didn't think I would ever hear more devastating news, but hearing, "I think this is LeA's last day of life," knocked that earlier statement right outta the ring.

That brings us to the last stage, Stage Four, for the remaining ten months of my daughter's life.

This stage was full of feeding tubes, specialty formulas, suctioning, deep suctioning, I can do deep suctioning. A mother should not know how to deep suction her child. Pneumonias. 36 doses of medicine daily. DNRs. Learning all about how to fill out a DNR on your 13 month-old child is not something a parent should do. With the help of many hours of private duty nurses, and a great set of family and friends, we were able to spend as much quality time as possible with our daughter as the final stages of her disease robbed her of life.

This story provides testimony to the significance of early detection. I will remind you again what I said earlier . . . I know a little boy born with the same disease ten days before my daughter. He was identified at birth, my daughter at ten months. Today he is in first grade and my daughter has been buried in her grave for five and 1/2 years.

Please help save other families from having to write stories like this.

The Children's Health Act of 2000 had promised to help fund states expanded newborn screening, but has yet to follow through with the money. States are left to their own means and I have heard that only 18 have decided that children's lives are worth the effort and cost.

I ask that this Committee encourage Congress to require states to inform parents in writing of the potential for their children to receive additional newborn screening tests that may not be required under State law. We must start by mandating that the hospitals educate parents on the availability of supplemental Newborn screening tests. This parental notification must be meaningful and

require informed consent. New Jersey has recently enacted this type of legislation. We must immediately put a plan in place for adding all testable/treatable diseases to every state in the nation's Mandatory Newborn Screening list.

The solution seems so simple. Available today are screening tests, technology, and treatments they are all available today, right now. We need to use them. We need to fix our current NBS system so that currently available resources are used to give every child the right to a healthy life.

Society for Inherited Metabolic Disorders
Mendel Tuchman M.D.
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Statement On Newborn Screening And Treatment Of Individuals With Inborn Errors Of
Metabolism Detected By Newborn Screening

Newborn Screening: Newborn screening, followed by appropriate long-term treatment, is a well-established strategy that effectively reduces disability and death from inborn errors of metabolism. As a result of many forces, including advances in technology and changes in public health systems, newborn screening and the systems of care for children identified by newborn screening are undergoing intense examination and change.

The SIMD: The Society for Inherited Metabolic Disorders (SIMD) is dedicated to improving scientific and public understanding about inborn errors of metabolism, and to promoting advances in the identification and care of those affected by inborn errors of metabolism.

Members of the SIMD are professionals actively involved in clinical or basic research or patient care directly related to inherited metabolic disorders. SIMD members are scientists, physicians, nutritionists, nurses, genetic counselors, and other health professionals working in patient care and research, in the laboratory and in the clinic, in academia, in public health, in private medical systems and in the biotechnology industry.

The SIMD and Newborn Screening: SIMD membership includes world leaders in newborn screening and in the care of patients with inborn errors of metabolism. Members of the SIMD serve on newborn screening advisory committees and task forces at the local, state and national level.

In 1998, the SIMD urged state health departments to examine their newborn screening profiles and consider expanding them by appropriate technology to include disorders of amino acids, organic acids and fatty acid oxidation for which treatment is beneficial. In 2003, the membership of the SIMD was surveyed for opinions on selected key issues in newborn screening and in the long term care of individuals with inborn errors of metabolism detected by newborn screening. The results of that survey were used to develop this statement, which has been approved by the SIMD Board and membership.

SIMD Survey Results:

A full report of the survey is available on the SIMD website at www.simd.org. This SIMD statement is based on the following key points: Respondents overwhelmingly agreed that screening of newborn infants for inherited (genetic) metabolic diseases should be expanded in the United States to include medium-chain acyl-CoA dehydrogenase (MCAD) deficiency and

other inborn errors of amino acid, fatty acid and organic acid metabolism detectable by analysis of amino acids and acylcarnitines using tandem mass spectrometry (MS/MS). However, SIMD respondents did not reach consensus about which criteria should be used to select conditions for an MS/MS screening panel. Most respondents agreed that each infant in the US should be tested for the same diseases, but a majority of respondents also noted that there are sometimes compelling reasons for variability in testing between populations (for example regional differences in incidence of conditions). Respondents strongly agreed that newborn screening should continue as a mandated state public health process, while envisioning flexibility in implementation including the possibility of regional newborn screening systems and the option to perform newborn screening testing in contracted laboratories that may be public or private. Respondents agreed that the director or medical director of the laboratory that is responsible for biochemical testing to confirm the diagnosis of an inborn error of metabolism should be certified in Biochemical Genetics by the American Board of Medical Genetics or have equivalent qualifications. Finally, while a majority of respondents agreed that newborn screening can be supported by private payers as well as by public funds, they also strongly agreed that there should be public assurance of support for immediate follow-up and long-term treatment to prevent death and disability.

Recommendations:

Screening of newborn infants for inherited (genetic) metabolic diseases should be expanded in the United States to include MCAD deficiency and other inborn errors of amino acid, organic acid and fatty acid metabolism detectable by MS/MS.

All infants in each state should be tested for the same panel of diseases, but programs should allow for flexibility when there are compelling reasons for variability in newborn screening testing between populations.

Newborn screening should continue as a mandated state public health process, with ultimate responsibility for a successful program resting with the state public health department.

Innovation through regional newborn screening networks and contracted public - private partnerships is likely to improve the quality and scope of newborn screening programs.

The diagnosis of a biochemical genetic disease in an infant detected through newborn screening should be confirmed in a laboratory where the director or medical director is board certified in Biochemical Genetics or has equivalent qualifications.

State public health departments should develop mechanisms to adequately fund newborn screening and the treatment of inborn errors of metabolism in those who are identified by newborn screening, including testing, reporting of results, confirmation of abnormal screening results, diagnosis, and comprehensive long- term treatment and evaluation.

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Infant through Adolescent Rights to Genetic Information

Market forces and economic incentives dictate that in order to receive the economies of scale in the genetic testing arena, larger numbers of newborns and children must be tested for an ever increasing number of heritable disorders and genetic diseases. These tests, most likely will not be individual tests, but rather *across the board*, testing with the particular disorder or disease

reported on to primary physicians and parents. This may leave a *balance* of genetic information on other disorders and diseases available for review at various times through a child's development and into adulthood.

For instance, a teenage girl may want to know her genetic information with regard to BRCA whereas her mother may not want to know this information. Given the information has implications and ramifications for both mother and the daughter, a conflict may arise. Committee recommendations built on the market and economic incentives for today may have consequences for future individual rights for vulnerable populations of children and their rights toward assent and informed consent.

Recommendation:

Build in *sunsetting* provisions for Committee recommendations made in light of today's rights, ethical issues, knowledge, and technologies. Legislative and statutory *renewal* time allows for the inclusion of changes in the social milieu, e.g. cultural change, new demographics, changes in rights and responsibilities for children and young adults and their access to their own genetic information.

Review of Social Forces which Impact Assumptions about Genetics in Populations

Historically, the field of genetics has always acknowledged differences in populations. From an ethnic perspective, this has included different disease frequencies in various populations, e.g. sickle cell anemia in African-American populations, *beta*-thalassemia in Mediterranean and Middle Eastern populations, and cystic fibrosis in Celtic populations. However, social and

cultural forces also influence populations and thus alter these disease frequencies, especially in the case of autosomal recessive disorders.

For instance, in some highly segregated African-American communities, the consanguinity rates may have risen due to the combination of high levels of incarceration of young black males, the resulting skew of male-to-female ratios, the phenomena of multiple matings, and the lack of knowledge about family histories and thus genetic backgrounds. Similar consanguinity issues arise as U.S. demographics change with an increase of Middle Eastern populations where cousin-cousin marriages are the norm. These demographic changes and levels of hypersegregation have distinct geographic perspectives. Examples are the inner city neighborhoods and rural towns with >95 percent African-Americans and cities with an increase of Middle Easterners. There are certain cities that have experienced extremely high growth in the Arab populations within the heading *Middle Eastern*.

In 2000, (576,000) Arabs (or 48 percent of the Arab population) lived in five states: California, Florida, Michigan, New Jersey, and New York. The Arab populations in Florida and Michigan experienced high growth rates as well as large numerical increases. The Arab population in Florida grew by 57 percent, from 49,000 to 77,000 between 1990 and 2000. One of the counties with the highest Arab population is Wayne County, Michigan and over 30 percent of the population in Dearborn, Michigan is Arab. <http://www.census.gov/prod/2003pubs/c2kbr-23.pdf> .

Recommendation:

Identify the social and cultural forces that influence populations, and thus alter the frequency of heritable disorders and genetic diseases. Identify new geographic areas where the combination of immigration and cultural mores may influence genetic and reproductive outcomes.

Cultural Aspects of the Medical Home Model and Infant/Child Health

In many cases, the *Medical Home Model* assumes a stable *one-place* geographic location for the newborn or child and the primary care physician. Immigration models and hidden cultural dynamics alter this assumption. For instance, in the case of immigration, many groups no longer come to the United States with the express plan to stay only in the United States. Many Mexican, Central American, and Caribbean populations are *dual nationals*, or migratory. Simply, they live in *both* the United States and their former countries with extensive visits back and forth. This necessitates an international component to the *Medical Home Model*, with links established between “medically-shared locales” [MSLs], rather than a unitary locale model.

For native U.S. populations, many ethnic groups have cultural habits that act in much the same way as *dual-nationalism* albeit domestic and interstate rather than international. These interstate treks have more of a gene-environment interaction component in disorders and diseases than those that are strictly heritable in the classic sense. For instance, African-Americans in the *North* and *Midwest* often send young children to visit extended family members in the “South” during the school vacation, summer periods. Given the high carcinogenic and toxic areas located in the South, usually near minority communities—children of color often are exposed to higher levels of lead contamination.

Yet, in many cases, pediatricians who serve communities of color and whose practice may be the medical home of the child in question do not take into consideration these cultural habits. With some African-American children, their *back home* visits to the South may represent 25 percent, (3 months) of a child's exposures to high lead contamination that takes place in an environment different from the location of the unitary medical home. These exposures often manifest as increases in blood lead levels during rapid childhood growth.

A similar situation exists for young woman exposed to high lead contaminations that repose in their bones. Bone lead mobilizes during times of increased bone turnover, such as during pregnancy and lactation. Again, blood lead levels show seasonal periodicity. Due to the environmental justice movement, a growing literature is developing on how these exposures and blood-lead mobilizations have an impact on conception, reproduction outcomes, fetal lead exposures and fetal neurobehavioral disorders.

Recommendation:

Develop *Medical Home* models that take into consideration *dual-nationalism* and migration patterns and forge relationships with the primary care physicians in those *medically-shared locales* that serve populations in which complex travel patterns are norm.

Inclusion of Indigenous and Traditional Knowledge and Social Capital in the Community-based Participatory Research Aspect of Heritable Disorders and Genetic Diseases in Newborns and Children

Currently, the United States is undergoing rapid demographic shifts. Old World populations in this country share living space with new immigrants. Scandinavian and German populations in

Minnesota and Wisconsin now share space with Somalians and Hmong. Polish populations in Hamtramck, Michigan share space with Arabs and Muslims. These new populations come to the United States eager to visit Western primary care physicians, but they still maintain ties with their traditional and indigenous healers, shamans, and curanderos. Western physicians, however, forfeit valuable information on beliefs, world views, practices, and community allegiances by classifying this information as magico-religious rather than medical information.

Recommendation:

Incorporate immigrants as well as their ethnic healers, shamans, curanderos, and the like into the practices of primary care physicians as collaborators rather than marginalized competition.

Immune Deficiency Foundation
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Mr. Chairman, thank you for the opportunity to present testimony on behalf of the Immune Deficiency Foundation (IDF).

IDF is the national nonprofit, voluntary health organization dedicated to improving the treatment and diagnosis of primary immunodeficiency diseases through research and education.

Headquartered in Towson, MD, IDF was founded in 1980 by a group of parents of primary immunodeficient children and their physicians who wanted to focus attention on the needs of the primary immunodeficiency community.

Genetically determined primary immunodeficiency diseases (PIDD) are disorders in which part of the body's immune system is missing or does not function properly. In contrast to secondary immune deficiency disease in which the immune system is compromised by factors outside the immune system, such as viruses or chemotherapy, primary immunodeficiency diseases are caused by inherited defects in the immune system. More than 140 different primary immunodeficiency diseases are now recognized. These disorders affect people of all ages, races, and both sexes. They are generally thought to be rare; however, neither the incidence nor prevalence of these disorders is known. This is due to the fact that there is no screening for any primary immunodeficiency disease at birth or during childhood or adulthood anywhere in the world. Thus, most patients are not diagnosed until they develop a serious infection, which certainly adversely affects the outcome of therapy. I suspect that these conditions are at least as common as the conditions currently screened for in newborn testing.

Based on IDF's 2002 National Patient Survey, the average length of time between the onset of symptoms in a patient and a definitive diagnosis of PIDD is 9.2 years. Some patients had been hospitalized up to 20 times before the diagnosis was made. In the interim, those afflicted may suffer repeated and serious infections and possibly irreversible damage to internal organs. Additionally, the number of permanent functional impairments increases dramatically the longer it takes to diagnose a patient with a primary immune deficiency. Many primary immunodeficient patients are able to maintain their health through regular infusions of intravenous immunoglobulin (IGIV). IGIV is a pooled plasma derivative that bolsters the patient's immune system. IGIV is administered intravenously, on average, every 3 to 5 weeks for the lifetime of

the patient. However, if primary immune deficiency diseases are not properly diagnosed and treated, they can lead to serious illness and early death.

In November 2001, a workshop was convened by the Centers for Disease Control and Prevention (CDC) to discuss ways to improve health outcomes among persons with primary immune-deficiency diseases. A multidisciplinary panel of persons knowledgeable in PIDD and public health met to identify and discuss public-health strategies that can be applied to primary immune-deficiency diseases and possibly for other genetic disorders. IDF actively participated in the process. As a result of that meeting, the CDC developed a strategic plan to address the problem of PIDD. The plan included the following four components:

- Public health assessment—application of traditional public health methods to assess the impact of PIDD on community health
- Population-based interventions—development, implementation, and evaluation of screening tests administered to newborns and clinical algorithms for early recognition of symptomatic persons to facilitate the earliest possible diagnosis and treatment
- Evaluation of screening and diagnostic tools—evaluation of screening and diagnostic tools to ensure their quality and appropriateness for identification of patients with PIDD
- Communication—communication with healthcare providers and the public to facilitate prompt and appropriate diagnosis and intervention.

In July 2002, NICHD, CDC, and HRSA held a workshop to explore the feasibility of developing newborn screening technology for Severe Combined Immunodeficiency Disease (SCID), also known as “bubble boy disease.” The goal of the workshop was to generate prioritized

recommendations, approaches, and strategies for developing advanced, cutting-edge technologies for effective newborn screening of SCID with blood spots. Another goal was to enhance collaboration and communication among basic scientists, biotechnologists, clinicians, epidemiologists, and policymakers so newly developed technology can be translated rapidly into effective newborn screening programs for SCID. IDF again participated actively in this meeting.

Infants with SCID have the most serious of the primary immunodeficiency diseases, with little or no immune system. They die from infection before their first or second birthday if not given immune reconstitution by bone marrow transplantation. SCID is a pediatric emergency.

If a SCID baby receives a bone marrow transplant in the first 3.5 months of life, the survival rate can be as high as 97 percent. However, the survival rate drops to 69 percent for infants who are transplanted after that age. The main causes for the drop in survival rate are serious infections SCID babies develop in the first few months of life. The condition can be detected at birth; however, it is currently not among the genetic diseases routinely tested for in newborn screening. For most SCID infants, the diagnosis is not made until 6.5 months of age on average, and most patients are critically ill by then. Nine forms of SCID have been identified in the past 11 years, caused by mutations of single genes. The most common form of SCID is X-linked recessive, a mutation inherited on the X chromosome. This form of SCID affects only boys, but accounts for 46 percent of U.S. cases.

My colleagues at Duke University Medical Center and I treat SCID patients via stem cell transplants derived from donor bone marrow, typically from a parent or matched sibling. Infants with SCID have a complete absence of T-cell function. T cells are white blood cells that are essential for normal function of the immune system. Because they lack T cells, SCID infants do

not need pretransplant chemotherapy, as they cannot reject the transplants. The donor bone marrow is processed to remove donor T cells, preventing the graft from attacking the recipient by a process known as graft-versus-host disease or GVHD. By taking out the T cells from the donor marrow, prophylactic treatments with immunosuppressive drugs to prevent GVHD are not necessary. Mature, donor-derived, T cells typically appear in SCID patients within 90 to 120 days after transplant. Of the 137 SCID patients I have treated at Duke, 106 (77 percent) are alive. Most are in good general health. The oldest is 22 years of age. All 16 recipients of marrow from perfectly matched donors and 90 of the 121 recipients of T cell-depleted marrow from parental donors are among the survivors. Twenty-four of the 31 deaths occurred from viral infections present at the time of diagnosis; there were no deaths from GVHD.

Of the 38 infants I have transplanted during the first 3.5 months of life, all but one (97 percent) survive, compared to 68 survivors among the 98 transplanted after that age (69 percent success). SCID patients who received stem cell transplants within the first 28 days of life developed earlier and more robust immune function than did those who received transplants later, with higher levels of T cell reconstitution and output from the thymus gland.

At a recent Newborn Screening and Genetic Testing Symposium sponsored by CDC, Dr. Jennifer Puck at the National Human Genome Research Institute announced that she had developed a technology that could be used to test newborns for SCID. Now that the technology has been developed, a pilot study should be done to begin screening all newborns for SCID at birth. Early treatment not only saves lives but also reduces costs. For example, a bone marrow transplant performed in a SCID infant in the first three months of life can cost less than \$50,000,

but the cost of care skyrockets up to millions of dollars in older SCID patients, primarily for treatment of their life-threatening infections, with less assurance of success.

Mr. Chairman, I cannot begin to stress enough the importance of early diagnosis and newborn screening for immunodeficiency diseases. While technology has not been developed to screen newborns for all primary immunodeficiencies, it has been developed for the most severe form, SCID. Dr. Harry Hannon and Dr. Robert Vogt of the Newborn Screening Branch at the National Center for Environmental Health at CDC have indicated their commitment to newborn screening for SCID. Dr. Vogt will be looking to the Immune Deficiency Foundation to develop a protocol for any newborns that test positive for SCID to receive the correct treatment in an expedited manner.

The Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children will be making recommendations to Secretary Thompson on grants and projects to help States and local public health agencies improve screening, counseling and health care services to newborns and children who have or are at risk for heritable disorders. Additionally, the Committee will be recommending the screening tests to be included in the Heritable Disorders Program.

Mr. Chairman, on behalf of the primary immunodeficiency community, I respectfully request that you and your fellow committee members include screening all newborns for SCID in your recommendations of the screening tests to be included in any and all programs this Advisory Committee has influence over, as well as any early diagnosis programs for the other primary immune deficiency diseases. Without an effective early intervention, the majority of SCID

babies die during the first years of life. The majority of patients with other forms of primary immunodeficiency diseases have guarded prognoses, being chronically ill and requiring intensive treatment. Screening methods have to be developed to detect these as well.

We look forward to working closely with you. Thank you.

Written public comment through Honorable Howard Coble's office:

Teri D. Broadstreet
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Dear Mr. Coble,

I am writing in reference to the neglectful medical care my 6 year old daughter received from birth, September 30, 1997, until February of 2002, from a local physician. Since being removed from their care, my daughter has been diagnosed with an extremely rare form of Trisomy 13 Genetic Syndrome, "Mosaic Trisomy 13". This has brought along with it, numerous disabilities and abnormalities to include: Atrial Septal Heart Defect, Duplicated Right Kidney Collecting System, Global Sensory and Behavioral Impairments, Polydactaly, and Developmental Delays. From birth Julie presented with many physical indicators symptomatic and inherent, not only to her disorder, but to a Full Blown Trisomy 13, as well s many commonly known Genetic Syndromes. In addition, she was at immediate High Risk, due to the fact I was of advanced maternal age, turning 39 years old October 14, 1997. At birth she presented as: Cyanotic, Required Resusitation, Respiratory Distress, Nuchal Cord X2, Transverse Simeon Palmer Creases, Polydactaly, Microcephaly, Epicanthal Folds, Ventral Hernia, Hemangiomas on her Forehead (with an unexplained Knot and Bruising), Broad Falt Nose, Small Slanted Close Set

Eyes, Lowset Ears, Thin Flat Upper Lip, Abnormal Flexion in her Fingers, Couldn't Suckle, Very Weak Cry, Below Average Birth Weight, an Undiagnosed Atrial Septal Heart Defect, and her Undiagnosed Kidney Defect. I am certain there must be other indicators that as just an "Uneducated Mon", having to decipher the Medical Jargon word by word, I haven't determined as yet.

Julie was seen by Dr. Winters and Dr. Reedy of Archdale Pediatrics, Archdale, NC from birth until she was 5 years old. My family expressed great concerns, even perfect strangers approached me in department stores stating, "She's so cute, does she have Downs syndrome?" I entrusted my child's complete life and total care to these physicians. Julie remained at and below 5th % height and weight from birth. She continued with eating issues (so vaguely recorded in her medical records "baby doesn't like formula"), excruciatingly painful constipation along with mysterious high fevers blown off as viruses, that I attribute now to her Kidney Disorder (presenting the exact same symptoms), dysmorphic features, motormental retardation, turning blue to the point of passing out when crying (Dr. Winters laughed off, telling me she hyperventilated, also stating her skin tones were just going to have blue undertones because she was a redhead), major eye issues (her first prescription was 6.5), developmental and behavioral issues etc. . . . Despite my many concerns, these physicians diagnosed her as completely normal, never intervening or referring her to higher levels of medical care such that major medical centers like Brenner's Children's Hospital, Wake Forest Baptist Medical Center, or Duke University can offer, disregarding every single one of my concerns. I've since discovered there was chatter amongst themselves, never in my presence, along with questionable xrays made the day Julie was born, with much vagueness, and many discrepancies in her medical records. How these physicians were totally and absolutely negligent in my child's care is appalling and completely departs from acceptable and prevailing medical practices. I will establish their

negligent treatment produced an extremely precarious safety risk, for my daughter's health and life, much greater than any prevailing treatment they should have provided.

I sought outside intervention through the Randolph County Health Department whose Nurse, Wendy Boggs RN, immediately observed dysmorphic features, as well as abnormalities in Julie's eating, gait, eyes, behaviors, delays etc. . . She immediately referred her for evaluations at Developmental Evaluation Center in Greensboro, NC and to an ophthalmologist. Dr. Ted Anderson at DEC, also, immediately observed her differences and referred her for genetic testing. This resulted in her initial diagnoses of "Mosaic Trisomy 13 since birth. As a result, because of High Risk with Trisomy 13, Julie was referred for further testing of her Brain, Heart, and Kidneys, where I also, initially discovered her Atrial Septal Heart Defect and Kidney disorder. Julie was 5 years old. As her health continued spiraling downward I requested all of my daughter's care to be transferred to Wake Forest Baptist Medical Center. Here, I thank, Dr. Joel Hutcheson Pediatric Urologist for giving my child the Gift of Life. He performed a Reimplantation of all of Julie's Urethra's, after discovering she had become resistant to 9 different antibiotics and developed an E-coli Infection, then a major Staff Infection due to her Kidney disorder. Urine was improperly routed, causing pooling and stagnating in her body since Birth. By the Grace of God, Dr. Hutcheson didn't find as much kidney damage as he had expected to find in a child that had been neglected for so long. Had this precarious, negligent, treatment continued Julie's kidneys would have shut down and she would have died. I am horrified in knowing, had my child died during these physicians care, Archdale Pediatrics, from birth until 5 years old, I would never have known the truth, as I suspect has happened to many families past, and ongoing (SIDS I suspect in my cases for example). Although we face many other issues, for the first time ever, Julie is currently symptom free, medicine free, and pain free, beginning to grow and thrive. She is an absolute joy and miracle child, despite her odds. A child

born with a Full Blown Trisomy 13, if she survives to become full term, 85% of these babies, do not survive 6 months old. Prognosis for Julie is unknown.

I feel my child has not been rendered proper evaluations, treatments, services, and habilitations due to the fact I must use the Medicaid System to fund her medical care, and, these physicians saw my child as a lost cause with no hope. With malice, on Julie's last visit to Archdale Pediatrics, Dr. Reedy beligerantly told me I was wasting my time, she didn't need genetic testing, didn't have a hernia, she was oppositional defiant and ADHD, there was no hope for my child, and, to be honest she had more problems than he knew what to do for. I threatened him that Wendy Boggs, RN for the Health Department would go over their heads if necessary as she had told me she would do so if she had to. At this point he angrily told me I would get them in the mail, and again I was wasting my time, as he slithered out the door. Dr. Chamberlain, Julie's current pediatrician, upon first glance of her medical records, stated, quote "If I were you, I would be madder than hell!" Dr. Anderson DEC, and Dr. Jewitt, Geneticist, WFU have also stated they don't understand how this happens time and again. I have discovered a whole society of families silently suffering as mine has through Networking and Support Groups. In addition, I've discovered a, "silent conspiracy", amongst physicians, covering each others tracks. As the parent of a precious little one, we endure enough pain and dejection at the loss of our dreams for our children. Small milestones become great triumphs.

I am seeking your assistance to present a bill to Congress to mandate more extensive evaluations of especially High Risk newborns. This disgusting, negligent practice must be stopped. Doctors must not be allowed to so arrogantly play "God", with our innocent children's lives. They must be made accountable to someone. I can find no laws to protect our children. A simple blood test at birth would prevent must needless pain and suffering, but, ultimately death.

I would appreciate an expedited reply on this matter. Thank you for your time and interest.

Business

Before concluding the meeting, the Committee addressed the topics of a future agenda and priority issues. In order to determine the frequency of future meetings (the legislation calls for two per year, but the Committee can adjust this schedule), the members spent some time defining issues to be considered on future agendas.

It was suggested that given the vast array of topics to be addressed, the Committee should focus, at least at first, on a few important issues and be pragmatic in areas in which there can be significant impact in the relatively short term. Committee members agreed that the consideration of a uniform panel, and the results of the ACMG contract, should be considered, as well as a future research agenda and emerging new technologies. It was requested again that the Committee receive more information on the ACMG project, which may not require waiting until the next meeting to provide information. Committee members requested a summary of the recommendations of the report once it has been delivered to HRSA, and of all public commentators, to determine common themes—for example, the idea of universal and equitable access to newborn screening, and also the idea of States notifying parents of additional testing that may be available. Committee members also requested an assessment of the status of the use of tandem mass spectrometry. It was also suggested that the Committee begin to consider the establishment of a strategic oversight group, similar to the National Vaccine Advisory Committee and the Advisory Committee on Immunization Practices.

Committee members then discussed the establishment of subcommittees to address some of the issues brought up during the meeting, and the possibility of obtaining other experts to sit in as non-voting consultants to the Committee, including a representative of State public health officials (through the Association of State and Territorial Health Officials), as well as State public health laboratories (through the Association of Public Health Laboratories). The Committee asked the chairperson to propose, in the interim between meetings, a possible substructure.

The members agreed to meet in person every three months, at least at the start, in Washington, DC. Dr. Howell thanked the members, speakers, and audience members for participating, and concluded the meeting.

We certify that, to the best of our knowledge, the foregoing meeting minutes of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children are accurate and correct.

/s/

/s/

R. Rodney Howell, M.D.
ACHDGDNC Chair

Michele A. Lloyd-Puryear, M.D., Ph.D.
ACHDGDNC Executive Secretary

These minutes will be formally considered by the Council at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.