Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Summary of 17th Meeting
February 26-27, 2009
Bethesda, MD

Prepared for:

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

Prepared by:

Altarum Institute
Washington, DC

March 2009

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 17th meeting at 8:34 a.m. on Thursday, February 26, 2009, at the Bethesda Marriott Hotel in Bethesda, Maryland. The meeting was adjourned at 2:10 p.m. on Friday, February 27, 2009. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments on February 26, 2009.

Committee Members Present

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CONTENTS

I. WELCOME, OPENING REMARKS

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
Professor, Department of Pediatrics
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University of Miami

Dr. Howell opened the meeting by welcoming two new representatives to the Committee: Dr. Kellie Kelm, the new ex officio representative to the Committee from the Food and Drug Administration (FDA), and Dr. Mary Willis, representing the U.S. Department of Defense. Dr. Willis was unable to attend this meeting, and Dr. Brian Hall was present as her representative. Dr. Howell thanked Dr. Rinaldo for his service, noting that his term as an Advisory Committee was ending, and presented him with a letter of appreciation and certificate from former Health and Human Services (HHS) Secretary Michael Leavitt. Dr. Rinaldo has agreed to continue serving the Committee as a consultant.

Next Dr. Howell reported that acting HHS Secretary Charles Johnson signed the Advisory Committee's new charter on February 12, 2009. The Newborn Screening Saves Lives Act of 2008 reauthorized the Committee for a 5-year period beginning on the date of enactment of the bill, so the Committee's new charter will expire on April 24, 2013. Under the new charter, a representative from FDA is added to the Committee as an ex officio member. The charter also calls for the addition of individuals with expertise in ethics and infectious diseases. The nomination forms for the individuals with expertise in ethics and infectious diseases will be released by HHS soon. Liaisons from the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) and the Secretary's Advisory Committee on Infant Mortality have been eliminated from the Committee under the new charter, but the charter encourages the Committee to work with various HHS groups in reviewing the scientific evidence and making recommendations for clinical prevention services. Finally, the new charter requires the Committee to publish an annual report on newborn screening in the United States that includes followup and treatment beginning in April 2011.

Proposed Letter from the Advisory Committee to the HHS Secretary Regarding Insurance Coverage of Medical Foods. Dr. Howell drew Committee members' attention to a letter from the Committee regarding medical foods, drafted by the Followup & Treatment Subcommittee, to be sent by the Advisory Committee to the HHS Secretary under Tab #5 in Committee members' briefing books. Committee members reviewed this letter electronically prior to the meeting, but the subcommittee chair Dr. Boyle said she would like to change the first paragraph to put it into the context of national health care reform efforts. The Committee asked to see the changes before voting on whether to approve the letter, and Dr. Boyle agreed to present a revised letter later in the meeting.

Approval of Minutes. The minutes of the Advisory Committee's 16th meeting (a virtual meeting via conference call) on November 24, 2008 (under Tab #5 in Committee members' briefing books) were approved with two corrections: (1) Page 8: change U.*S. Preventative Services* to U.S. Preventive Services; (2) Page 9: change *hermatopoietic* to hematopoietic.

Committee's Response to SACHGS Survey on Genetics Education and Training. Dr. Howell drew Committee members attention to information provided in response to a survey from the SACGHS by the Advisory Committee on Heritable Disorders in Newborns and Children about the Advisory

Committee's interest in and efforts related to the genetics education and training of health professionals under Tab #5 in Committee members' briefing books. He noted that the Genetic Alliance had conducted, and would be distributing information about, an informal survey among members of the Advisory Committee on Heritable Disorders in Newborns and Children regarding their satisfaction with the Committee's level of emphasis on genetic and genomic education.

Advisory Committee's Revised Operating Procedures. Dr. Howell asked Advisory Committee members to review the Committee's revised operating procedures ("ACHDNC: Policies and Procedures for the Operation and the Development of Recommendations for Screening Newborns and Children for Heritable Disorders and for the Heritable Disorders Program") under Tab #16 in their briefing books, noting that the Committee would vote on whether to approve these procedures later in the meeting.

New HRSA Administrator. Dr. Howell reported that Dr. Mary Wakefield, one of the nation's top rural health experts, will soon be replacing Dr. Betty Duke as the administrator of the Health Resources and Services Administration (HRSA). Dr. Wakefield is likely to be supportive of the Committee's efforts.

II. UPDATE ON THE NEWBORN SCREENING USE CASE AND RELATED DEVELOPMENTS

Alan E. Zuckerman, M.D.
Personalized Health Care Initiative
U.S. Department of Health and Human Services (HHS)
Primary Care Informatics Program Director
Georgetown University School of Medicine

Dr. Zuckerman gave an update on progress toward the development of health information standards to support the generation and exchange of electronic information related to newborn screening. The "Newborn Screening Detailed Use Case" and the "Newborn Screening Use Case Coding and Terminology Guide," both developed by the subgroup on newborn screening of the American Health Information Community's (AHIC) Personalized Healthcare Workgroup, were released to the public by the HHS Office of the National Coordinator for Health Information Technology (ONC) on December 31, 2008 and are available online.

- ***Newborn Screening Use Case:***
  http://www.hhs.gov/healthit/usecases/documents/NBSDetailedUseCase.pdf
- ***Newborn Screening Use Case Coding and Terminology Guide (for comments):***
  http://transparency.cit.nih.gov/screening/

The Health Information Technology Standards Panel (HITSP) is using these documents to help it identify and harmonize standards for vocabularies, data elements, datasets, and technical standards that vendors can adopt to support the exchange of electronic information related to newborn screening. The weekly meetings of HITSP's Population Perspective Technical Committee that is working on the specifications are open, and public participation is encouraged. Public participation will be important to keep HITSP from narrowing its focus or leaving out the needs of people working in the field of newborn screening.

It is expected that the newborn screening use case will be accepted by the HHS Secretary through the new HITSP, when that is constituted around December 2009, and that newborn screening will enter into certification and commercial products in July 2011. A webinar was held with the Association of Public Health Laboratories to prepare for using the electronic newborn screening lab reports. A document for the newborn screening use case that will deal with privacy issues under the Health Insurance Portability and Accountability Act (HIPAA) and the Clinical Laboratory Improvement Amendments (e.g., sharing newborn screening results with nonordering providers and sharing results across state lines) is expected soon.

The AHIC Personalized Health Care Workgroup will be ending its tenure in December 2009, and the plan is that the National Library of Medicine's (NLM) Unified Medical Language System (UMLS) will become the permanent and publicly accessible home for work on developing terminology and coding pertaining to newborn screening. Dr. Zuckerman and his colleagues have proposed that the NLM use the "Newborn Screening Use Case Coding and Terminology Guide" and the newborn screening subset of LOINC® codes (used to report laboratory and other clinical observations) developed by the Personalized Health Care Workgroup as a starting point. Dr. Clement McDonald from the Regenstrief Institute in Indianapolis and the NLM handed out copies of two documents: (1) the "Newborn Screening" page in the NLM's Genetics Home Reference Web page (http://ghr.nlm.nih.gov/nbs); and (2) a list of newborn screening terminology and associated LOINC® codes. He stated that the NLM would like the Advisory Committee's help in keeping the terminology and codes up to date.

The next important coding and terminology activity will be building quality measures and outcomes datasets for long-term followup. This work is more complex than the work that has been done on to date. It essentially involves defining quality measures (which may be patient based, practice based, or population based) and specifying codes for the various observations that will be gathered. The use of a service-oriented architecture will allow the extraction of data from other clinical records (often in a deidentified way) to get at the critical measures needed for long-term followup.

The Children's Health Insurance Program Reauthorization Act of 2009 [Section 1139A(d)(1)(D) and 1139A(f)] calls for a demonstration project of the impact of a model electronic health record format for children as part of quality measures for child health. Newborn screening could be a foundational component of this. A standard national child health record should begin with ordering a newborn screening and collecting birth parameter and carry the newborn screening results forward in this context.

Questions & Comments

Dr. Boyle asked Dr. Zuckerman to elaborate on the Quality Use Case developed by ONC. Dr. Zuckerman said the Quality Use Case was done in 2007 to allow automated review of electronic health records to extract quality measures. The hope is that that clinical care systems will be automated and will meet research and quality measurement needs. HITSP has identification protocols and pseudo-anonymization protocols that that allow selected individuals, when needed, to reidentify a person of interest. These were developed for biosurveillance and other public health activities.

Dr. Watson observed that all the recent changes in entities involved in health information technology at the federal level recently are rather confusing—the move from AHIC to the AHIC Successor, and the changes in the economic stimulus package enacted in mid-February 2009 going back to two HHS-based structures. Dr. Zuckerman said that the important thing to understand is that there is going to be a transition and that two new committees governed by the Federal Advisory Committee Act will set priorities: (1) the Health Information Technology Policy Committee will try to identify what we should

be doing and trying to implement; and (2) the Health Information Technology Standards Committee will provide a review on usability and intent to use health information standards (it will not replace HITSP, which does the day-to-day work on standards, or standards development organizations like HL7). One of the few things spelled out clearly in the new legislation is that there will be an initial set of standards designated by the HHS Secretary December 2009 (some of which will incorporate existing standards and some of which may allow other approaches or make modifications). What is ready in newborn screening in December 2009, therefore, will impose significant constraints on the use of certain types of funds and on certain time frames to migrate to the new standards.

III. COMMITTEE PROCESS: REPORT FROM THE DECISION CRITERIA & PROCESS WORKGROUP

Bruce Nedrow (Ned) Calonge, M.D., M.P.H.
Chief Medical Officer and State Epidemiologist
Colorado Department of Public Health and Environment
Committee Member

Dr. Calonge described revisions to the Decision Criteria & Process Workgroup's report, which includes a recommended approach and decision matrix for the Committee to use when considering whether to add conditions to the uniform newborn screening panel. Dr. Calonge then sought the Committee's approval of the workgroup's report, with the understanding that minor revisions to some sections of the report remain to be made (e.g., minor editing to the introductory section, a decision about how much of the decision regarding certainty of net benefit needs to be discussed in the body of the report vs. an appendix, fine-tuning of the decision matrix, and work on the study design/quality appendices).

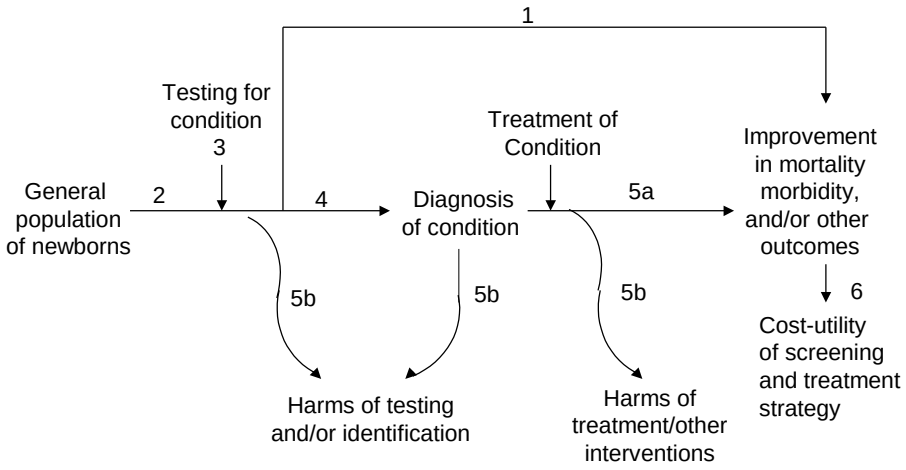
Proposed Analytic Framework for the Committee's Decisions. The analytic framework recommended for use by the Advisory Committee when considering whether to include conditions on the recommended uniform newborn screening panel consists of six key questions:

- **Key Question #1 (overarching question)**: Is there *direct evidence* that screening for the condition at birth leads to improved health outcomes for the infant or child to be screened, or for the child's family? Dr. Calonge said the best direct evidence would be randomized clinical trials (RCTs) involving screen-detected infants, but for many conditions considered by the Advisory Committee, such evidence is not likely to be available; hence, the answer to this question will usually be "No." In cases where direct evidence is not available to answer Question 1, however, Questions 2 through 6 allow for the development of a chain of evidence that, if adequately addressed by research, can be used to support an Advisory Committee's recommendation regarding the inclusion of a condition on the uniform newborn screening panel.
- **Key Question #2:** Is there a *case definition* that can be uniformly and reliably applied? What are the clinical history and spectrum of disease of the condition, including the impact of recognition and treatment?
- **Key Question #3**: Is there a *screening test* or screening test algorithm for the condition with *sufficient analytic validity*? (Analytic validity refers to the technical, laboratory accuracy of the test in measuring what it is intended to measure.)

- **Key Question #4:** Has the *clinical validity of the screening test* in combination with the diagnostic test or algorithm been determined and is that validity adequate?
    - Is the evidence sufficient to conclude that we know what the clinical validity (ability to accurately predict the development of symptomatic or clinical disease) is?
    - Is level of clinical validity sufficient to justify testing?
- **Key Question #5:** What is the *clinical utility of the screening test* or screening algorithm?
    - 5a. What are the benefits associated with the use of the screening test?
    - 5b. What are the harms associated with screening, diagnosis, and treatment?
- **Key Question #6:** How *cost-effective is the screening, diagnosis, and treatment* for this disorder compared to usual clinical case detection and treatment?

Proposed Approach for the Committee in Weighing the Evidence.

Figure 1—Analytic Framework



The Decision Criteria & Process Workgroup recommended that the Advisory Committee do the following when weighing the evidence:

1. Evaluate the quality of available studies (e.g., study design, threats to internal validity and threats to external validity/generalizability to populations other than those studied).
2. Determine adequacy of evidence for each of the eight key questions. Saying that the evidence is adequate mans that the observed estimate or effect is likely to be real rather than explained by flawed study methodology, and the Advisory Committee concludes the results are unlikely to be

strongly affected by the results of future studies. The workgroup recommends that the Committee use six critical appraisal questions to determine adequacy of the evidence:

- Do the studies have the appropriate research design to answer the key question?
- To what extent are the studies of high quality (internal validity)?
- To what extent are the studies generalizable to the U.S. population (external validity)?
- How many studies and how large have been done to answer the key question (precision of the evidence)?
- How consistent are the studies?
- Are there additional factors supporting

Proposed Decision Matrix for the Committee to Use in Making Recommendations. The Decision Criteria & Process Workgroup recommended that the Advisory Committee consider three questions when translating the evidence into recommendations. First, what is magnitude of net benefit (are the benefits of screening, diagnosis and treatment minus the harms significant)? Second, what is overall adequacy of the evidence (does the evidence overall meet the standards for having adequate quality)? Third, what is the certainty of net benefit/harm (is the Committee certain that the research supports a conclusion that benefits exceed harms or not)?

The Decision Criteria & Process Workgroup further proposed that the Advisory Committee use four general categories when making recommendations about whether to add a condition to the uniform newborn screening panel:

1. **Recommend adding the condition to the core panel.** The Committee has sufficient certainty of *significant net benefit* to recommend adding the condition to the core newborn screening panel.
2. **Recommend NOT adding condition to the core panel.** The Committee has sufficient certainty of *no net benefit or of net harm.*
3. **Recommend not adding the condition to the core panel now and recommend additional studies**. The evidence is insufficient for the committee to make a recommendation to add the condition to the core panel, but the *potential for net benefit is compelling* enough to recommend *additional studies to fill in the evidence gaps*.
4. **Recommend not adding the condition to the core panel now**. There is *insufficient* evidence for the Committee to make a recommendation to add the condition to the core panel, and there is insufficient evidence of potential net benefit to lead the Committee to want to make a strong recommendation regarding pilot studies. (An example might be a condition for which there is currently no treatment and no evidence of other benefits that might be realized through early detection.)

Proposed Matrix for Committee's Decisions			
Category	**Recommendation**	**Level of Certainty**	**Magnitude of Benefit**
1	Recommend adding the condition to the core panel	Sufficient	Significant
2	Recommend NOT adding the condition to the core panel	Sufficient	Zero or net harm
3	Recommend not adding the condition to the core panel but recommend additional studies	Insufficient, but the potential for net benefit is compelling enough to recommend additional studies to evaluate	Potentially significant, and supported by contextual considerations
4	Recommend not adding the condition now	Insufficient, and additional evidence is needed to make a conclusion about net benefit	Potentially significant or unknown

Questions & Comments

Dr. Rinaldo recommended changing the order of recommendations in the proposed decision matrix from best to worst (1,3, 4, 2), so that the present recommendation #2 (NOT adding the condition to the panel) would be last. Dr. Calonge agreed to make this change. Dr. Rinaldo also said that if the answer to Key Question #1 is always going to be "No" (because RCTs involving screen-detected infants will not be available), that question might as well be removed from the analytic framework.

Dr. Buckley asked Dr. Calonge to clarify what the heading "Level of Certainty" in the third column of the decision matrix, pertains to: the recommendation or the level of the evidence. Dr. Calonge explained that it refers to "Level of Certainty of Net Benefit." Dr. Nancy Green, speaking from the audience, asked Dr. Calonge what would happen in cases where there is a benefit but it is very small and comes at a great cost. Dr. Calonge said the situation might be rare but the Committee would have to wrestle with that.

Dr. Jeffrey Botkin, also speaking from the audience, asked whether the framework accounted for multiplex platform testing that provides information about conditions that your may not be specifically targeting. Dr. Calonge said his understanding in working with Dr. Howell and the leaders at HRSA was that the Advisory Committee performs a "condition-specific review" so the Committee's recommendation is around the condition—not the test. Dr. Watson said he could understand that each condition would be looked at independently by the Committee but added that the costs of screening for additional conditions using tandem mass spectrometry (MS/MS) would be incremental. Dr. Calonge agreed, saying that this fact would be taken into account in cost-effectiveness analyses.

Dr. Trotter moved to accept the report of the Decision Criteria & Process Workgroup presented by Dr. Calonge, and Dr. Buckley seconded his motion. The Committee approved the following motion unanimously:

- **MOTION #1 (APPROVED): The Advisory Committee accepts the framework proposed in the report by the Decision Criteria & Process Workgroup, with the understanding that minor revisions to the report still must be made.**

Dr. Calonge said that the Decision Criteria & Process Workgroup planned to submit its report for publication and might put the appendices online. Dr. Howell said he hoped the report would be published.

IV. SCID NOMINATION: EVIDENCE REVIEW, PUBLIC COMMENTS, AND COMMITTEE DISCUSSION

Severe combined immunodeficiency (SCID) was nominated for inclusion on the uniform newborn screening panel in 2008, and the Advisory Committee asked the external Evidence Review Workgroup, chaired by Dr. James Perrin, to prepare a review of the evidence for this condition. In this session, Dr. Ellen Lipstein, gave an overview of the Evidence Review Workgroup's report on the evidence for SCID. Subsequently, four individuals from the public offered comments on the SCID nomination. Finally, the Advisory Committee began discussing what recommendations to make with respect to SCID's inclusion on the uniform newborn screening panel.

A. External Evidence Review Workgroup's Final Draft Report on SCID

Ellen Lipstein, M.D.
Fellow, Harvard Pediatric Health Services Fellowship
Center for Adolescent and Child Health Policy
MassGeneral Hospital for Children

Dr. Lipstein explained that SCID is a rare congenital immune deficiency characterized by the absence of both cellular and humoral immunity due to defects in T-cell production and function, and in some cases by defects in B-cells or natural killer cells. The rationale for the Evidence Review Workgroup's review of SCID was that infants born with SCID develop severe infections as their protection from maternal antibodies wanes and die early in childhood unless they receive disease-specific treatment. Methods to screen infants for SCID have been developed, and early identification and treatment of SCID by screening may decrease death and illness associated with SCID and its treatment.

The Evidence Review Workgroup's final draft report on the evidence for SCID was submitted to the Advisory Committee in January 20, 2009, and included under Tab #9 in Committee members' briefing books. The full report includes a description of methods, a summary of the evidence, tables highlighting key data from abstracted articles, materials provided to interviewees, a conflict-of-interest form, and a bibliography of all identified articles.

Key Questions Addressed in the Review of the Evidence on SCID. Dr. Lipstein explained that the Evidence Review Workgroup's report was based on a systematic review of the literature and an assessment of critical unpublished data from key investigators to address the following questions pertaining to SCID, emphasizing the questions related to screening and benefits of early treatment:

- What is the natural history of SCID and are there clinically important phenotypic or genotypic variations?
- What is the prevalence of SCID and its variations?
- What methods exist to screen newborns for SCID? How accurate are those methods? What are their sensitivity and specificity?
- What methods exist to diagnose individuals with positive screens?

Key Findings in the Review of the Evidence on SCID. The Evidence Review Workgroup's key findings with respect to SCID included the following:

- Without curative treatment, newborns with SCID develop severe infections leading to early death.
- SCID affects at least 1/100,000 newborns in the United States, and the incidence of SCID may be higher than measured via case ascertainment because some infants may die prior to receiving a definitive diagnosis.
- Methods to screen newborns for SCID include the use of real-time polymerase chain reaction (PCR) technology to measure the number of T-cell receptor excision circles (TRECs) in DNA extracted from newborns' screening specimens (dried blood spots). Population-based screening trials of screening newborns for SCID using measurement of TRECs are under way in Wisconsin and Massachusetts, but no population-based screening trial has been completed. Data regarding the accuracy of other methods to screen newborns for SCID are not available.
- Three modes of treatment have been investigated for SCID in the last 20 years: allogenic hematopoietic stem cell transplant (HSCT), enzyme replacement therapy, and gene therapy. HSCT has been used as a treatment for SCID since 1968 and has been shown to greatly decrease mortality and morbidity associated with SCID. Enzyme replacement therapy has been used as therapeutic option for SCID patients with ADA deficiency, a specific type of SCID. Gene therapy has been tried for the treatment of X-linked SCID and ADA-deficiency SCID.
- Some evidence supports the benefit of pre- or early symptomatic treatment with HSCT compared to later treatment. Potential harms associated with HSCT include the development of autoimmune hemolytic anemia and leukemia.

Critical Evidence Needed to Inform Screening Recommendations for SCID. Evidence Review Workgroup believes that several critical pieces of information are needed to inform the Advisory Committee's screening recommendations for SCID:

- **Screening for SCID**
    - What method should be used for finding cases of SCID? No systematic method of case finding exists for SCID. Pilot screening programs currently underway should be a means of systematically identifying cases of SCID in screened populations. The new consortium of treatment centers—the U.S. Immunodeficiency Network—may also facilitate systematic case finding.
    - What is the accuracy of screening for SCID? Current data are limited. Early data from Wisconsin using measurement of TRECs in newborns' dried blood spots suggests a low

false-positive rate. TRECs are consistently absent or present in low numbers in newborns with SCID.

- What is the feasibility of screening for SCID? Wisconsin's experience susggests screning is feasbile, and Massachusetts has just initiated a screening pilot for SCID. No data exist regarding the ability of other newborn screening programs to offer SCID screening.

- **Treatment for SCID**
  - What is value of early treatment for SCID? Evidence is limited. [Note: Dr. Nancy Green, speaking from the audience after Dr. Lipstein's presentation, observed that there was some disagreement in the Evidence Review Workgroup about the magnitude of the potential benefit from early diagnosis through screening and treatment.]
  - What is the cost-effectiveness of screening and treatment for SCID? Cost-effectiveness analyses using measured costs and utilities, as well as sensitivity analyses are needed.
  - How adequate are available treatment centers for SCID? The number of centers in the United States and their capacity to provide treatment for SCID is unclear. No current data address variation in SCID treatment success among treatment centers. Future data from the U.S. Immunodeficiency Network and the Center for International Blood and Marrow Transplant Research may provide evidence for treatment availability and variation.

B. Public Comments Related to SCID

Public comments about whether the Advisory Committee should vote to recommend SCID's inclusion on the uniform newborn screening panel were provided by the following individuals: Dr. Jennifer Puck, Dr. Mei Baker, Barbara Ballard, and Marcia Boyle. The full text of their comments appears in Appendix A.

1. Jennifer M. Puck, M.D.
SCID Nominator
Department of Pediatrics
University of California–San Francisco

Dr. Puck, the nominator of SCID, said she thought newborn screening for SCID is a terrific opportunity to save babies with SCID, whose condition otherwise may not be recognized until it is too late to prevent death or irreparable harm. She also noted that there was some exciting new data coming from the U.S. Immune Deficiency Foundation and SCID Family Group.

2. Mei W. Baker, M.D.
Assistant Professor, Department of Pediatrics
Science Advisor, Newborn Screening Program
Wisconsin State Laboratory of Hygiene
University of Wisconsin–Madison

Dr. Baker stated that SCID is ideally suited for newborn screening for several reasons: (1) the prevalence is estimated to be 1 in 66,000; (2) effective treatment is available, and early identification and intervention result in significantly improved survival; and (3) confirmation tests are readily

available. In January 2008, Wisconsin began a pilot study of the SCID screening among all newborns born in the state using polymerase chain reaction (PCR) technology to quantitate T-cell receptor excision circles (TRECs) in newborns' DNA extracted from blood spots. Wisconsin's year 2008 experience, summarized in the report of the external Evidence Review Workgroup, indicates that screening newborns for SCID is feasible with minimal false positives. TRECs are found in normal naïve T cells, which are consistently absent or low in all SCID patients. Quantitating the number of TRECs on newborn dried blood spots identifies infants with primary immunodeficiency.

3. Barbara Ballard
Parent and Administrator
SCID Network of Families

Ms. Ballard urged the Advisory Committee to make testing newborns for SCID a standard of care. Because SCID is a disease which cannot be seen or identified at birth without a blood test, children who have SCID like Ms. Ballard's son are born looking and acting seemingly normal, but opportunistic infections early in life can severely disable or kill them. When Ms. Ballard's son Ray caught his first cold, he ended up in the pediatric intensive care unit with a form of pneumonia. At age 1 while on a ventilator in a pediatric intensive care unit, he received a bone marrow transplant to treat his SCID and survived. Many infants with SCID do not. Unfortunately, however, Ray suffered medical complications due to SCID that have left him, now age 15, with severe lung damage and scarring, gastrointestinal damage that requires him to be fed by enteral and parenteral means, and deaf. His medical costs maxed out a $2 million insurance policy by the time he was 5 years old. Early diagnosis could have given Ray a life without many of these ongoing challenges. Finally, Ms. Ballard noted that screening newborns for SCID is essential to identify children with SCID so that they are not given live virus vaccines (e.g., rotavirus vaccine) early in life that may case irreversible harm or death.

4. Marcia Boyle
President and Founder
Immune Deficiency Foundation

Ms. Boyle, the founder of the Immune Deficiency Foundation, urged the Advisory Committee to vote to add SCID to the uniform newborn screening panel. She reported that Immune Deficiency Foundation, a national patient organization that engages in advocacy, education, and research to improve the diagnosis, treatment, and quality of life of persons with primary immune deficiency diseases, recently conducted a special survey of a national sample of 208 SCID families to understand their experiences with diagnosis and treatment. The survey's findings indicate that early diagnosis and treatment of SCID are critical to prevent the development of opportunistic infections and other medical complications that are fatal or cause irreparable harm to affected infants' health.

C. Committee's Discussion and Decisions Regarding the Nomination of SCID to the Recommended Newborn Screening Panel

At Dr. Howell's request, Dr. Vockley led the Committee's discussion of the nomination of SCID. Before the general discussion began, however, Dr. Howell asked Dr. Buckley, an expert in SCID and other genetically determined immunodeficiency diseases, whether she had any comments to make. Dr. Buckley noted that she and her colleagues at Duke University had prepared a paper that has not yet been published on the long-term followup of SCID patients who had received bone marrow transplants. In that study, they compared patients who received transplants under 3 ½ months of age vs. those who were not transplanted until later. The median survival was the same in both groups, but the patients who

received transplants under age 3½ months were considered healthy by their families. Dr. Buckley said the leading cause of death in infants with SCID is viruses, including live chickenpox vaccine.

Dr. Vockley then went through each of the six key questions in the basic analytic framework recommended in the Decision Criteria & Process Workgroup's report that the Committee had just voted to approve and gave his own answers to each of the questions to get the ball rolling:

- **Key Question #1 (overarching question)**: Is there *direct evidence* that screening for the condition at birth leads to improved health outcomes for the infant or child to be screened, or for the child's family? Answer: No. There is no randomized clinical trial (RCT) of newborn screening for SCID vs. not screening providing direct evidence.
- **Key Question #2:** Is there a *case definition* that can be uniformly and reliably applied? What are the clinical history and spectrum of disease of the condition, including the impact of recognition and treatment? Answer: Yes. There is a good case definition. All cases of SCID are serious and deadly early in life if not treated. Genetic heterogeneity is not relevant to screening. All treatments (bone marrow transplant, gene therapy, enzyme replacement) are effective.
- **Key Question #3**: Is there a *screening test* or screening test algorithm for the condition with *sufficient analytic validity*? Answer: No. There are no data yet on lab variability in the performance of the screening test, the sensitivity and specificity of the test, quality control, assay robustness, or the ability to transfer tests to other labs. Pilot screening studies using DNA testing (TREC quantitation) in Wisconsin (70,000 newborns screened) and Massachusetts have not yet detected any infants with SCID.
- **Key Question #4:** Has the *clinical validity of the screening test* in combination with the diagnostic test or algorithm been determined and is that validity adequate**?** Answer: No. A test that measures the number of TRECs in newborns' DNA seems most robust, but no cases of SCID have yet been identified in population screening with the test. Diagnostic testing for SCID is highly reliable and readily available.
- **Key Question #5:** What is the *clinical utility of the screening test* or screening algorithm?
    - 5a. What are the benefits associated with the use of the screening test?
    - 5b. What are the harms associated with screening, diagnosis, and treatment?
    - **Answer:** The benefit associated with screening newborns for SCID using DNA testing (TREC quantitation), if diagnosis and treatment for SCID occur prior to age 3½ months or the onset of symptoms—namely, the reduction of morbidity and mortality among infants found to have SCID—is compelling. No harms associated with SCID screening, diagnosis, and treatment have been identified or are anticipated.
- **Key Question #6:** How *cost-effective is the screening, diagnosis, and treatment* for this disorder compared to usual clinical case detection and treatment? Answer: There is minimal formal analysis, but screening for SCID is probably cost-effective based on the cost of a bone marrow transplant vs. the treatment of SCID diagnosed late.

In summary, Dr. Vockley said, he believes that the Evidence Review Group's report shows that there are strong reasons for screening for SCID, an excellent diagnostic test, and compelling data on treatment for SCID; however, there is inadequate evidence of the analytic validity of the screening test. Given some of the gaps in the evidence about SCID, Dr. Vockley recommended that the Committee make the

following recommendation from the proposed matrix for the Committee's decisions (Note: In the final version of the Decision Criteria & Process Workgroup's report, Category 3 below will become Category 2):

- **Recommend not adding the condition to the core panel now and recommend additional studies**. The evidence is insufficient for the committee to make a recommendation to add the condition to the core panel, but the *potential for net benefit is compelling* enough to recommend *additional studies to fill in the evidence gaps*.

Committee's Discussion of Key Question #1 (direct evidence of improved outcomes with screening). Committee members disagreed about whether there is direct evidence that screening for SCID leads to improved outcomes—and about what constitutes direct evidence. Dr. Calonge said the definition of direct evidence is there is a randomized clinical trial (RCT), and if there is no RCT of newborn screening for SCID vs. not screening, the answer to Key Question #1 should be "No." That does not mean, however, that the Committee will end up recommending that SCID not be added to the uniform newborn screening panel, though, because Questions 2 through 6 allow for the development of a chain of evidence that can be used to support another recommendation.

Dr. Rinaldo said that if the answer to Key Question #1 is always going to be "No," then it should just be eliminated. Dr. Rinaldo said he would argue that there had been a screening test for SCID for the last 26 years, and that was the birth of a first child with SCID who usually died or suffered terrible damage. So the second case of a newborn with SCID in a family who was diagnosed at birth because of the recognized risk and received treatment early is evidence that screening for SCID leads to improved outcomes. Dr. Calonge stated that he would be nervous about an evidence-based group redefining direct evidence, especially when it was not needed.

Dr. Rinaldo also said that he was very concerned about morbidity and mortality related to the use of live vaccines in children with undiagnosed SCID. There appears to be harm from *not* screening newborns for SCID. Dr. Alexander agreed, saying that he found it hard to say that the answer to this question is "No," especially given the evidence from the Duke program cited by Dr. Buckley, along with the clear indication that live virus vaccines can be fatal to infants with undiagnosed SCID.

Committee's Discussion of Key Question #2 (case definition). Dr. Kus said that he thought Key Question #2 was confusing because it included two questions. Dr. Vockley explained that the second question is just asking for information to answer the first question. Dr. Calonge explained that Key Question #2 is intended to clarify whether we know what the condition we want to test for is and what the condition does with and without treatment.

Committee members agreed that there is a very good case definition of SCID. Dr. Anne Comeau, speaking from the audience, also pointed out that the case definition applies at the time that the newborn screening result or diagnosis. One does not have to wait 3 years for it.

Dr. Rinaldo questioned Dr. Vockley's assertion in answering Key Question #2 that all treatments for SCID— hematopoietic stem cell transplant (HSCT), gene therapy, enzyme replacement—are similarly and highly effective. The SCID nominator Dr. Jennifer Puck, participating by phone, confirmed that gene therapy is a highly experimental form of therapy for SCID. Dr. Lipstein clarified that the Evidence Review Group concluded that some evidence supports the benefit of pre- or early symptomatic

treatment with HSCT compared to later treatment, but the evidence for early treatment is not as complete as the evidence of HSCT for SCID.

Committee's Discussion of Key Question #3 (analytic validity of the test). Dr. Calonge explained that the analytic validity of the test for SCID is more critical to the implementation of the test than it is to whether the Committee recommends adding SCID to the uniform newborn screening panel. A test must have analytic validity in order to have clinical utility. Dr. Comeau and Dr. Getchell stated that the analytic validity of the DNA test for SCID is really pretty good. In order to measure analytic validity of the test for SCID very well, however, one needs good quality control materials that can be sent around to all the state screening programs—and such materials currently do not exist. Dr. Chen agreed. Dr. Vogt indicated that the Newborn Screening Branch at the Centers for Disease Control and Prevention (CDC) will make such materials ready in the near future.

Dr. Mei Baker, speaking from the audience, reported Wisconsin's pilot SCID newborn screening program, which has used a DNA test (TREC quantitation) to screen 70,000 newborn blood spots in its first year, has not detected a classic SCID case yet. Wisconsin's program has had a false positive rate with the DNA test for SCID of 0.05 percent (0.002 percent in full-term babies and 0.028 in premature babies). It has not had any false negatives for SCID. Dr. Bob Vogt, speaking from the audience, indicated that the test for SCID seems to detect non-SCID primary immunodeficiencies as well as SCID. The pilot SCID screening program in Wisconsin has identified three babies with DiGeorges syndrome. Dr. Buckley said that the DNA test for SCID may pick up things other than SCID, but it will not pick up anything that does not need treatment.

Dr. Anne Comeau, the principal investigator of the pilot SCID newborn screening program in Massachusetts, speaking from the audience, reported that Massachusetts had screened 4,000 newborn specimens for SCID. The pilot screening program in Massachusetts has identified one baby with in utero exposure to teratogen who does not have thymus and is working up one baby right now who may be positive for SCID. She said it appears that screening for SCID is something that states can do, especially if they get training in the technical capacity for SCID screening such as that offered by the National Newborn Screening and Genetics Resource Center (NNSGRC).

Committee's Discussion of Key Question #4 (clinical validity of the test with the diagnostic test). Dr. Chen and Dr. Vockley noted that neither of the two ongoing pilot population-based SCID newborn screening programs (in Wisconsin and Massachusetts) has identified a single baby who has been diagnosed with SCID. For that reason, Dr. Chen said he thought it would be very difficult for the Committee to recommend adding SCID to the uniform newborn screening panel at this point.

Dr. Rinaldo asked whether any retrospective testing and analyses had been done on a blinded group of blood specimens collected from children subsequently diagnosed with SCID. Dr. Puck said that she had done some of this and unerringly picked out the SCID samples. Dr. Rinaldo said the DNA test for SCID appears to be a very good test and noted that the Newborn Screening Translational Research Network (NBSTRN) being developed could facilitate the validation of assays conclusively in a matter of days. Dr. Chen emphasized that testing a known or blinded group of blood samples from patients with SCID is very different from looking for 1 case of SCID in 100,000 samples in statewide, population-based newborn screening program.

Committee's Discussion of Key Question #5 (clinical utility, benefits and harms associated with screening diagnosis, and treatment). Dr. Vockley stated that he agreed with Dr. Green's interpretation

of the data presented by the Evidence Review Group that there is compelling evidence that early diagnosis and treatment of SCID is beneficial. Dr. Howell said the benefits associated with treatment of SCID are spectacular.

Several Committee members, including Dr. Boyle, Dr. Calonge, and Dr. Kus, challenged Dr. Vockley's assertion in answering Question #5 that there are no harms associated with screening, diagnosis, or treatment have been identified or are anticipated. They noted that the Evidence Review Group had reported harms associated with SCID treatment that should not be minimized, although it is important to weigh the potential harms against the very significant potential benefits.

In response to a concern raised by Dr. Calonge about the possibility of providing stem cell transplants to children who screen positive for SCID but do not actually have SCID, Dr. Buckley explained that a newborn who screens positive for SCID can be readily diagnosed as having SCID or not having SCID with certainty. Dr. Comeau noted that there is an "incredibly minimal" possible harm to very low birthweight babies referred for flow cytometry who have to give blood to confirm a diagnosis of SCID.

Committee's Recommendation. Dr. Vockley summarized the Committee's conclusions as follows: There appear to be strong reasons for screening for SCID. There are gold standard diagnostic tests for SCID. There are compelling benefits of treatment for SCID. Yet there are important gaps in the information about screening for SCID. He asked: What should the Committee recommend with respect to SCID's inclusion on the uniform newborn screening panel?

Ms. Monaco said that as a parent she would rather see slight imperfections in the screening for SCID than to allow babies with SCID to go undetected and end up with lifelong problems. Dr. Rinaldo noted that if 1in 100,000 babies has SCID, then 40 children will be born in the United States with SCID and 35 will die in the next year, adding that he could not live with these statistics. Dr. Rinaldo also noted that change is slow, and until SCID is recommended for inclusion on the uniform panel, states will have no desire to screen for SCID. Dr. Burton agreed with Dr. Rinaldo that the Committee should recommend SCID's inclusion on the uniform newborn screening panel.

Dr. Getchell said that she is not comfortable that the DNA test (TREC quantitation) for SCID is ready for distribution to state newborn screening programs. Once the Advisory Committee makes a recommendation, then it is up to state screening programs to figure out how to implement the test and pay for it, and Dr. Getchell said she does not believe states are ready for that or that the test is ready for the states, given the lack of quality control materials. Dr. Chen said his organization represents physicians who have to worry about the other 99,999 children out of 100,000 who do not have SCID. He does not think that the discussion of clinical utility and of the potential harms of screening, diagnosis, and treatment has been adequate. Dr. Nancy Green, speaking from the audience, emphasized the importance of having the Committee discuss assistance to states or to regions in setting up high-quality screening programs for SCID. Dr. Kus strongly agreed about the importance of planning for the implementation of SCID screening in the states.

Dr. Alexander said he thinks that the DNA test for SCID is going to work and would like to recommend SCID's inclusion in the newborn screening panel, but expressed concerns that moving ahead with a recommendation for full-blown newborn screening for SCID when the pilot newborn screening programs in Wisconsin and Massachusetts have not yet identified a single case of SCID would damage the Advisory Committee's credibility. In addition, Dr. Alexander suggested that the Newborn Screening Translational Research Network (NBSTRN) now being developed with funding from the National

Center of Child Health and Human Development (NICHD) might be used to speed up the process of getting answers to the critical remaining questions about the SCID test. Dr. Fleischman said he thought that it was incumbent upon the Advisory Committee to define very carefully in a list what it would take in order for the Committee to recommend SCID's inclusion on the uniform newborn screening panel.

Dr. Howell said it was his sense that the Committee would hope to get SCID screening started as soon as possible but some critical information is needed before the Committee can recommend SCID's inclusion on the uniform newborn screening panel. He asked for a recommendation from the Committee that would capture the urgency of getting SCID on the uniform panel soon along with some plans to get the necessary information to permit that.

Dr. Alexander moved that the Committee make the following recommendation for SCID from the proposed matrix for the Committee's decisions: **Recommend not adding the condition to the core panel now and recommend additional studies**. The evidence is insufficient for the committee to make a recommendation to add the condition to the core panel, but the *potential for net benefit is compelling* enough to recommend *additional studies to fill in the evidence gaps*. The Committee voted to approve this motion.

- **MOTION #2 (APPROVED): The Advisory Committee's recommendation with regard to the nomination of SCID to the uniform newborn screening panel is recommendation #3: "Recommend not adding the condition now but encourage additional specific studies."**

Dr. Howell appointed a small group headed by Dr. Vockley to develop a list of specific information that must be developed for SCID before the Committee can recommend SCID's inclusion on the uniform newborn screening panel and asked the group to report to the Committee the following morning.

V. UPDATE FROM NICHD-NIH ON THE NEWBORN SCREENING TRANSLATIONAL RESEARCH NETWORK (NBSTRN) AND OTHER INITIATIVES

Duane Alexander, M.D.
Director
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)**
National Institutes of Health (NIH)
Committee Member

Dr. Alexander updated the Advisory Committee on key initiatives related to newborn screening at the National Institute of Child Health and Human Development (NICHD) and the National Institutes of Health (NIH), including progress in developing the Newborn Screening Translational Research Network (NBSTRN).

Development of the Newborn Screening Translational Research Network (NBSTRN). One of the three components of NICHD's initiative in newborn screening, which began about 4 years ago, is to build a research infrastructure that is large and potentially national in size and scope to facilitate the

introduction of new screening tests and treatments in a research mode to gain knowledge as quickly as possible so that no potential data on rare disorders would be lost.

In developing the NBSTRN, NICHD has five major objectives (1) to provide material resources (e.g., dried blood spots) for researchers; (2) to provide research sites (e.g., states or regions) for piloting new tests; (3) to provide sites for gathering standardized information on the natural history of untreated disorders, genotype-phenotype correlations, as well as outcomes with different treatments as they come along; (4) to provide research sites for testing new treatments in a research context; and (5) to set up disease registries with built-in privacy protections for studies of treatment and natural history of specific diseases. When considering how best to develop the NBSTRN, NICHD realized that the HRSA-funded Regional Genetic Service and Newborn Screening Collaboratives coordinated by the American College of Medical Genetics (ACMG) was a ready-made resource.

In September 2008, therefore, NICHD awarded the ACMG a 5-year, $13.5 million sole source contract to serve as the NBSTRN Coordinating Center. The statement of work calls for the NBSTRN Coordinating Center to do the following:

1. Establish an organized network of state newborn screening programs and clinical provider networks.
2. Develop, implement, and refine a national research informatics system for investigators that links with existing national clinical networks.
3. Establish and administer an efficient, reliable repository of residual dried blood spots (virtual or physical)
4. Provide expertise and support to researchers about the regulatory requirements for their work (e.g., informed consent, institutional review boards [IRBs], and variations in these among states and localities).
5. Facilitate research on the developing new methods and technologies by maintaining close contact with the scientific and research communities.
6. Facilitate research on screened and treated patients to identify effectiveness of treatments and long-term outcomes.
7. Have the capacity and expertise in statistics and the design of clinical trials to help researchers who need help in those areas.
8. Facilitate the timely dissemination of research findings.
9. Establish a research steering committee that includes people with expertise in health care, public health, ethics, and science to make recommendations about proposals that would get access to the NBSTRN.
10. Nominate research projects for possible access to the NBSTRN.

Dr. Alexander said that the ACMG has reported several accomplishments with respect to the development of the NBSTRN, including the establishment of an organized network for research, workgroups of state laboratory officials and clinical centers, a steering committee that will meet on April 6-7^{t,h} 2009, to discuss how workgroups will function and the development of a virtual repository of residual and dried blood spots, as well as the development of initial approaches for developing an informatics and communication systems (possibly using the cancer Bioinformatics Grid known as

caBIG as a model and resource), the establishment of an information technology research working group that will meet in June 2009, and the development of laboratory and practice standards and guidelines and care plans (current practices) related to newborn screening. A meeting was held in Denver on February 21-22, 2009, to discuss a national consensus on care plans for metabolic diseases that are the framework for many of these new activities. The NBSTRN is ready to receive requests for blood spots and requests to do pilot studies from the Advisory Committee.

Support for Research on New Screening Methods and Treatments. NICHD's initiative in newborn screening includes two components in addition to the creation of the NBSTRN: (1) increasing the number of conditions that are screened for by developing new screening methods and treatments for conditions detectable via newborn screening; and (2) developing and testing new treatment approaches for congenital disorders that have the potential to be detected via newborn screening but for which there is no effective treatment.

NICHD has entered into two contracts for projects on the development of novel screening methods. One project on the expansion of tandem mass spectrometry (MS/MS) to measure enzyme activity for lysosomal storage disorders—Fabry disease, Pompe disease, and mucopolysaccharidosis 1 in newborn screening samples—by Ronald Scott, University of Washington, has had many delays, primarily due to institutional review board (IRB) concerns. The other project, a project on the validation of a new multiplex buffer for assays for thyroid, cystic fibrosis, and congenital adrenal hyperplasia, the development and optimization of the IL-7 assay for severe combined immunodeficiency (SCID) and utilization of Luminex fluorescent bead array technology for biotinidase genotyping by Kenneth Pass at the New York State Department of Health/Wadsworth Center, is progressing. These two contracts are expiring, and NICHD will be issuing new requests for proposals for additional projects related to novel screening methods.

NICHD and other NIH institutes have also funded several projects to develop and test new treatment approaches for congenital disorders that have the potential to be detected via newborn screening but for which there is no effective treatment.. Funded projects include the following: novel treatment and screening strategies in heritable gamma-hydroxybutyric aciduria; pharmacologic chaperone therapy in mouse Gaucher disease and therapy of neuronopathic Gaucher disease; N-carbamylgutamate in the treatment of hyperammonemia (urea cycle disorders); optimization of drug-like compounds for spinal muscular atrophy (SMA); innovative therapies and clinical studies for classic galactosemia; stimulating SMN2 exon 7 inclusion with short RNAs (SMA); therapeutic opportunities in SMA; restoration of hearing in connexin mutant mice; a preclinical trial of intratympanic antivirals for CMV-related hearing loss; and anaplerotic therapy in propionic academia.

The National Children's Study. Finally, Dr. Alexander described plans for the National Children's Study mandated by Congress in the Children's Health Act of 2000. The purpose of the study is to look at environmental influences on children's health and development. The study will be follow 100,000 children recruited over 4 to 5 years during their mother's pregnancy or earlier and then followed until about age 21. It is the largest study of its type ever undertaken . The study must be this large to draw inferences about links between environmental exposures of various types and medical or psychosocial/behavioral outcomes. NICHD and other federal partners have engaged in extensive planning for this study, and the study is now in the field in two of the seven sites involved in piloting the current protocol for the study; the other five pilot sites will join the study in April 2009.

All children who are picked up in newborn screening programs will be identified and included in the National Children's Study, so there will be more detailed information about the followup of these children will be available than has been available in the past. In addition, the National Children's Study will have DNA from all the children, their siblings, and parents to make it possible to look at gene-environment interaction issues. The study will have sufficient computer capacity to look at the multiple exposures that children have to environmental substances or situations and how these interact with the children's genetic constitution.

Questions & Comments

In response to a question, Dr. Watson clarified that the meeting on April 6-7, 2009, would not be a NBSTRN steering committee meeting, but a meeting of a number of people representing state newborn screening programs an others to talk about the use of residual biospecimens to support research, quality assurance, etc. That meeting is closed because the room is too small to accommodate more people. Dr. Watson stated that the meeting of the NBSTRN steering committee would be held on April 16-17, 2009. That meeting will not be closed, but space will be limited, and there will not be open participation for anyone who chooses to come. The meeting of the bioethics group in June will just be a small working meeting.

Dr. Lloyd-Puryear asked whether entities not funded by NIH that wanted to carry out research using the NBSTRN (e.g., to look at SCID) should apply to NIH or to the NBSTRN Coordinating Center at ACMG. Dr. Alexander replied that these details are still being worked out.

Dr. Kus asked when some information would start to come from the National Children's Study. Dr. Alexander said that the study was recruiting participants in waves of 4 years, so it would take 4 years to recruit all the newborns. Data and datasets would be made available to interested investigators periodically through the study.

VI. REPORTS FROM HRSA AND CDC-FUNDED LONG-TERM FOLLOWUP PROJECTS AND THE NBSTRN COORDINATING CENTER

In this session, three research projects investigating different models for the long-term followup of newborns with conditions detected via newborn screening with funding from the Health Resources and Services Administration (HRSA) and Centers for Disease Control and Prevention (CDC) were described:

- A project by the University of Massachusetts Medical School on long-term followup of newborns in New England
- A project by the California Department of Health Services on long-term followup in California
- A project by the University of Utah's Division of Medical Genetics on long-term followup in Utah

The session ended with a presentation by Dr. Watson from the American College of Medical Genetics (ACMG) on the project to develop the Newborn Screening Translational Research Network (NBSTRN) funded by the National Institute of Child Health and Human Development (NICHD). As reported earlier by Dr. Alexander, the ACMG headed by Dr. Watson has a 5-year contract to serve as the NBSTRN Coordinating Center.

A. Long-Term Followup of Newborn Screening Conditions in New England

Anne Marie Comeau, Ph.D.
Deputy Director
New England Newborn Screening Program
University of Massachusetts Medical School

Dr. Comeau reported that the project for long-term followup of newborns with conditions detected via newborn screening in New England builds on existing databases of the region's long-standing collaborative newborn screening networks without having to replicate systems. Massachusetts now has formal regulations that ensure that screening programs will be able to collect long-term followup data, including data on long-term outcomes. A new booklet is used to notify parents that if their newborns are found to have conditions detected via newborn screening, they will be followed throughout their lives.

The project for long-term followup of newborns with conditions detected via newborn screening in New England project has a long-term followup workgroup with newborn screening coordinators from the six participating states: Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, and Vermont. The goals of the project are public health quality assurance, public health quality improvement, and public health engagement in research. The project is focusing on newborns screened and found to have hemoglobinopathies, cystic fibrosis, and metabolic conditions. Three areas have been identified for data collection and quality improvements.

Dr. Comeau provided a few examples of ongoing work. She noted that much of the data on long-term followup of children with conditions detected via newborn screening in New England is coming from primary care providers, who care for these children, rather than metabolic clinics or hemoglobin clinics.

Questions & Comments

Dr. Geleske observed that in view of the fact that many children with metabolic conditions are being followed up by primary care providers, perhaps metabolic clinics should develop models of comanagement. Dr. Comeau replied that that there is not much comanagement in the New England states now, except perhaps in Massachusetts.

B. California Newborn Screening Program: Long-Term Followup Data System for Metabolic Disorders

Lisa Feuchtbaum, Dr.P.H, M.P.H.
Research Scientist IV
Genetic Disease Screening Program
California Department of Health Services

Dr. Feuchtbaum explained that California's long-term followup data system for metabolic disorders is basically a public health surveillance system that follows children diagnosed with conditions detected via newborn screening through age 5. California data system was built on the state's Web-based, secure, Health Information Portability and Accountability Act (HIPPA)–compliant information system used for short-term followup newborns with conditions detected via tandem mass spectrometry (MS/MS) screening.

An annual survey instrument known as the Metabolic Center Annual Patient Summary (MCAPS) permits the assessment of long-term followup. MCAPS collects data for each child with a metabolic condition at the end of each year of the child's life through age 5 on the following:

- Availability of ongoing care and management (e.g., clinical followup status, services provided by the metabolic center in the previous year, total number of visits to the metabolic center in the previous year, treatments/therapies/strategies prescribed in the previous year)
- Patients' clinical outcomes and development (e.g., has the patient been symptomatic in the previous year, persistent health problems/symptoms in the previous year, assessment of patients' development and function in specific areas, as well as a global health assessment)
- Impacts on the utilization of health care (e.g., total number of hospitalizations, emergency room visits with length of stay and reason for admission, in the previous year)

Dr. Feuchtbaum provided several examples of some of the information gained by using California's long-term followup data system to demonstrate its utility in assessing the availability of ongoing care management, clinical outcomes in developmental assessment, and health care utilization by children with conditions detected via newborn screening.

Questions & Comments

Dr. Buckley noted that there seemed to be considerable attrition in California's followup system. Dr. Feuchtbaum explained that the system is based on providers completing cases as children's birthdays roll around. At this point, the data are largely cross-sectional. Every time she goes to the system, there are more data. She imagines that in 5 or 6 years, there will be thousands of cases that can be looked at prospectively.

C. Utah's Pilot Project Using the Surveillance Infrastructure of the State Birth Defects Programs for Long-Term Followup

Nicola Longo, M.D., Ph.D.
Professor and Chief
Division of Medical Genetics
University of Utah

Dr. Longo reported that a project at the University of Utah, with funding from CDC, is integrating data on children with disorders detected by newborn screening into Utah's birth defects registry, which collects data on the utilization of services and health outcomes.

Utah's long-term followup project began with a pilot study with the HRSA-funded Mountain States Genetics Network to define what parameters should be collected in long-term followup of children identified with conditions detected by newborn screening. Then templates were designed for use in clinical settings to collect disease-relevant information. In September 2008, an abstractor using all available data (including data in other hospitals' locations) collected data on data on all conditions Utah has been screening for since the expansion of newborn screening since 2006. These data were reviewed by a physician to make sure that the diagnosis was correct, and the data were integrated into Utah's statewide birth defects registry in December 2008.

The data collected in Utah on newborns with conditions detected via newborn screening include common elements (e.g., demographic information, functional outcome, how the children are growing, what their IQ is, whether they have an occupation), as well as information from the screening lab, information about how the diagnosis was confirmed, clinical encounters with the metabolic clinic or primary care physician, findings of morbidity, use of early intervention and other types of services. Utah has started a pilot project to enter all patients with the relevant conditions, in addition to those identified by newborn screening. They want to study patients with glutaric academia type I in particular to compare data for patients identified by newborn screening and patients identified clinically.

Dr. Longo ended by saying that long-term followup of newborns with conditions detected via newborn screening is essential for understanding the natural course of rare disease and the effects of screening and treatment. He noted that data from multiple centers must be combined to obtain statistically significant results and that longitudinal data covering multiple years are needed to truly evaluate health outcomes. Incorporating data long-term followup data on newborns into birth defect surveillance programs, where present, builds on an ongoing infrastructure with public health and research capabilities and offers many advantages: sustainability, quality, alignment of targets and resources, and effective use of funds.

D. Report from the NBSTRN Coordinating Center at the American College of Medical Genetics (ACMG)

Michael S. Watson, Ph.D., FACMG
Executive Director
American College of Medical Genetics (ACMG)
Representative to the Committee

As reported in Dr. Alexander's presentation, the National Institute of Child Health and Human Development (NICHD) awarded the American College of Medical Genetics (ACMG) a 5-year, $13.5 million contract to serve as the Newborn Screening Translational Research Network (NBSTRN) Coordinating Center.

Development of an Organized Network of Screening Programs and Clinical Providers. Dr. Watson said that one of the tasks of the NBSTRN Coordinating Center is to establish an organized network of state newborn screening programs and clinical centers. He noted that much of the data for the NBSTRN will come from clinical care providers such as metabolic and genetic clinics who diagnose and manage infants and children with conditions detected via newborn screening and from patients and patients' families, because they are at the heart of many of the activities of interests. The NBSTRN will provide a system for developing much better evidence than ever before on genetic metabolic conditions, hemoglobinopathies, hearing loss, cystic fibrosis and other conditions that newborns are, or potentially could be, screened for at birth.

The NBSTRN will collect and use data that are relevant to three major domains:

- **Patient care domain.** Clinical providers that diagnose and manage patients with conditions that can be detected via newborn screening document information in patients' medical records. Thus, clinical provider networks and their patients are able to provide detailed data on patients' demographics, diagnosis, and management. The clinical provider networks being formed under the NBSTRN will tie together the physicians who see individuals with conditions that can be

detected via newborn screening. Clinical care settings are a good place to obtain patients' consent to participate in long-term followup, too, because only about 12,000 newborns (of the 4.2 million newborns that undergo screening in the public health system each year) are true positives and managed in clinical care settings.

- **Public health domain**. The NBSTRN will collect long-term followup data after newborn screening that is relevant to public health questions, including whether children who screen positive subsequently get a confirmed diagnosis and appropriate intervention in time to achieve optimal health outcomes, the clinical history of diseases (the basis for next-generation therapeutics on which clinical trials will have to be run). Such data are also useful in epidemiological and surveillance studies and health services research and figuring out whether conditions such as SCID are amenable to population-based screening. The NBSTRN can use data from population-based biospecimen repositories maintained by public health programs.
- **Research and clinical investigation domain.** The NBSTRN will collect data from clinical provider networks on the clinical histories of conditions that newborns are screened for or might be screened for. It will also have data from patient registries and patient biospecimen repositories.

Development of a National Research Informatics System. The second main task of the NBSTRN Coordinating Center is to develop, implement, and refine a national research informatics system for investigators that links with existing national clinical networks. The development of an informatics system for the NBSTRN to support patient registry development, protocol development (standardized protocols and data languages), data warehousing, with minimal duplication of work and expense is critical. The NBSTRN steering committee will make a decision about the appropriate infrastructure, but Dr. Watson has been talking to the National Cancer Institute (NCI) for over a year about the possibility of modifying its cancer Biomedical Informatics Grid (caBIG™), in which NCI has invested nearly $150 million in the last 4 years, to serve as a health information infrastructure for the NBSTRN.

Development and Maintenance of a Repository of Dried Blood Spots. A third task of the NBSTRN Coordinating Center is to establish and administer an efficient, reliable repository of residual dried blood spots (virtual or physical). NICHD is interested in putting out requests for applications (RFAs) to investigators to address issues that can improve newborn screening.

Facilitate Research to on Treatments and Long-Term Outcomes. A fourth task of the NBSTRN Coordinating Center is to facilitate research on screened and treated patients to identify effectiveness of treatments and long-term outcomes. The NBSTRN Coordinating Center plans to operate in a highly protocol-driven activity, much like the National Cancer Cooperative Study Groups. Some of the HRSA-funded Regional Genetics and Newborn Screening Collaboratives have been working very closely together to develop their databases and care plans. The NBSTRN Coordinating Center supported a meeting held in Denver on February 21-22, 2009, to discuss a national consensus on care plans for metabolic diseases developed by the regional collaboratives. It is working with the National Library of Medicine (NLM) on taking these care plans and getting them into languages that can operate appropriately in the health care environment. Efforts are being to minimize duplication through collaboration to develop an infrastructure that meets everyone's needs.

Questions & Comments

Dr. Calonge asked Dr. Watson whether he thought the integration of electronic health data related to newborn screening, treatment, and followup might occur sooner than the adoption of electronic health records by primary care physicians. Dr. Watson said yes, there has been more progress in health information technology pertaining to genetic information than in primary care. NCI's caBIG™ is in 50 medical centers around the United States and can serve as "middleware" for the NBSTRN. Dr. Watson also reported that there are ongoing discussions about developing a national IRB that understands issues of newborn screening and followup to support the NBSTRN.

Dr. Howell said he hoped that the NBSTRN would be an enormous asset and observed that the NBSTRN might be used for research on screening newborns for severe combined immunodeficiency (SCID). He agreed that the infrastructure of caBIG™, which allows people to access data from many, many sites in a confidential way, offers many advantages. Natasha Bonhomme representing Ms. Terry from the Genetic Alliance added that what is being developed in the NBSTRN appears to be the foundation of something that could eventually link to patients' electronic health records.

VII. RESEARCH ISSUES RELATED TO INFORMED CONSENT AND INSTITUTIONAL REVIEW BOARDS (IRBS)

This session included presentations on two mechanisms for the protection of human subjects of research—peer review by institutional review boards (IRBs) and requirements for informed consent from the subjects of research—that are critical to multicenter or national studies of newborn screening, treatment, and followup:

- An overview of the U.S. regulatory framework governing the protection of human subjects in research involving children by Dr. Jeffrey Botkin
- A presentation on IRBs and how to create arrangements for multicenter or national research protocols by Dr. Edward Bartlett from the Office for Human Research Protections (OHRP)
- A presentation on how to deal with challenges that arise in the realm of the protection of human subjects of research in multicenter research related to newborn screening by Dr. Alan Fleischman

A. Regulation and Oversight of Research Involving Children

Jeffrey R. Botkin, M.D., M.P.H.
Professor of Pediatrics & Medical Ethics
Associate Vice President for Research
University of Utah

Dr. Botkin explained that in 1979, after abuses by scientific researchers that endangered the health or the life of their subjects without their permission were exposed, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published the Belmont Report, in which it articulated three ethical principles that should govern research on human subjects. The three principles were (1) respect for persons (requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy); (2) beneficence (an obligation to maximization of benefits

and reduction of risk); and (3) justice (fairness in distribution, according to several widely accepted formulations of just ways to distribute burdens and benefits).

Mechanisms for Protecting Human Subjects. At present, the mechanisms for protecting human subjects of research in the United States include peer review by IRBs (multidisciplinary panels, with lay participation); requirements for informed consent from the subjects of research; and professional integrity on the part of researchers.

The U.S. Code of Federal Regulations has two regulatory frameworks for the protection of human subjects of research:

- **"The Common Rule"** (**CFR Title 45, Part 46, Subpart A).** The Common Rule established requiring the review of human subjects research by institutional review boards (IRBs) applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency that takes appropriate administrative action to make the policy applicable to such research. The Common Rule has been adopted by 17 federal agencies that conduct human research and is very hard to change.
- **Food and Drug Administration (FDA) regulations (CFR, Title 21, Part 50).** These regulations are relevant to human subjects' research under FDA regulation of drugs and devices. These regulations are nearly identical to the Common Rule, with some notable exceptions (including the lack of provision for a waiver of informed consent).

Institutional Review Boards (IRBs). IRBs exist at academic institutions, at public health institutions (e.g., health departments, National Institutes of Health), and at research collaboratives (i.e., a central IRB for a research collaborative), and as commercial entities (e.g., Western IRB). Institutions sign a Federal Wide Assurance (FWA) with the U.S. Department of Health and Human Services that commits them to following federal regulations governing human subjects' research. Federal regulations provide a floor for IRB, but IRBs maybe more stringent and create local policies and procedures for domains not covered by the regulations. Thus, there is considerable variation among IRBs. IRBs are permitted to defer authority to a separate IRB.

IRBs use the following definitions when considering research on human subjects:

- **Research** means a systematic investigation—including research development, testing, and evaluation—designed to develop or contribute to generalizable knowledge (there is usually an expectation of publishing the results). There are a couple of grey areas:
    - Use of a novel therapy by a physician in the attempt to benefit the individual patient—this is not research, but IRBs struggle with retrospective chart review in such situations.
    - Quality assurance/quality improvement—if an individual is trying to improve quality, it may collect data prospectively and have an intervention without this being considered research, but if there is a plan to publish results, then the effort is considered research and needs an informed consent process.
- **Human subject** means a living individual about whom an investigator (whether professional or student) conducting research obtains (a) data through intervention or interaction with the individual; or (2) identifiable private information (e.g., medical records, tissue samples, databases containing individually identifiable data).

Research Not Considered Human Subjects Research. The Common Rule exempts some research activities from requirements of human subjects research. Exempt activities (identified in Section 46.101(b) of Subpart A) are defined as activities in which the only involvement of human subjects will be in one or more of the following categories (as determined by the IRB):

- Research conducted in established or commonly accepted educational settings...
- Research involving the use of educational tests…
- Research involving the use of educational tests (cognitive, diagnostic, aptitude achievement), survey procedures, interview procedures,..
- Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study public benefit or service programs...

Approvable Research With Children (CFR, Title 45, Part 46, Subpart D). Four categories of approvable research with children identified in the Code of Federal Regulations are the following:

- §404—Research not involving more than minimal risk (e.g., a psychological exam).
- §405—Research involving more than minimal risk but offering prospects of direct benefit to the individual subject (even life-threatening if proportional benefit).
- §406—Research with greater than minimal risk and no prospect of direct benefit but likely to yield generalizable knowledge about the subject's disorder or condition (e.g., a protocol using bronchoscopy in children with cystic fibrosis following colonization with *Pseudomonas*). This is more complicated and controversial.
- §407—Not otherwise approvable research. This research must be approved by an expert panel and the Secretary of Health and Human Services (HHS). The approval process has been streamlined but it is still hard.

In the first two categories of research with children (§404 and §405), the consent of one parent of a child is required. In the latter two categories (§406 and §407), the consent of two parents of a child is required. In all four categories, the child's assent is generally required (the IRB determines age for assent, and the child's assent can be waived for beneficial purposes).

Waiver of Informed Consent Under the Common Rule. One difference between the Common Rule and the FDA regulations governing human subjects research is that the Common Rule allows for a waiver of informed consent if the following four of the following criteria are met (45 CFR 46.116d):

1. The research involves no more than minimal risk to the subjects.
2. The waiver or alteration would not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.

4. When appropriate, the subjects can be provided with additional pertinent information after participation.

Dr. Botkin concluded by presenting a case that illustrates the dilemmas for IRBs in figuring out whether research is human subjects research requiring informed consent or meets the criteria for a waiver.

Questions & Comments

Dr. Dougherty questioned the ethics of asking patients to check off a box on patient history form consenting to the use of their samples for research. Dr. Botkin said that that approach is increasingly utilized. Both nationally and internationally, there is increasing interest in using databases associated with individual care, electronic medical records combined with public health databases, etc., and institutions around the country are aggressively pursuing tissue banking. Often that research does not involve the full panoply of elements of informed consent required by federal regulations. Basically, federal regulations say that eight elements are required for informed consent, and there are a couple of other things that the IRB is supposed to think about. Checking off a box would not be considered adequate consent for the conduct of research. If the IRB believes that research involves no more than minimal risk to the subjects, however, it may say consent can be "waived or altered." In addition, researchers do stuff with samples that nobody ever gave consent for. An IRB decides things on a case-by-case basis. If researchers test a sample for a BRCA1 mutation on an identifiable sample, they must get consent. If the sample is anonymized, the consent requirement might be waived.

Dr. Dougherty said she thought perhaps individual doctors or clinical practices were creating registries, so they could publish a case series about their work. Dr. Botkin said setting up a registry for the purpose of conducting research is an enterprise requiring IRB approval. Accessing a tissue bank to use specimens for research also requires IRB approval. However, IRBs approve retrospective chart review (case series of patients) without individual consent all the time.

Dr. Watson asked what threshold is used to determine whether a specimen in a registry is identifiable. Dr. Botkin said the Common Rule says that a sample is considered identifiable if its source is "readily identifiable by the investigator." The Health Insurance Portability and Accountability Act (HIPAA) requires the removal of 18 specified potential identifiers for a specimen to be considered deidentified.

B. Regulatory Options for Multiple IRBs and Alternative IRB Models

Edward Bartlett, Ph.D.
International Human Research Liaison
Division of International Activities
Office for Human Research Protections (OHRP)
U.S. Department of Health and Human Services

Dr. Bartlett discussed federal regulations governing cooperative research projects involving more than one institution. He explained that when federal regulations pertaining to the protection of human subjects of research were written in the 1980s, most research was performed at a single institution. Usually, if there were five sites where research was being conducted, each institution's IRB did a full review and left the investigator to try to reconcile the different recommendations. This process might take 1 to 2 years. Actually, though, federal regulations are fairly permissive in terms of the IRB arrangements research institutions are allowed to use in cooperative research projects.

The Common Rule (CFR Title V, Part 46, Subpart A, §46.114) specifies several mechanisms that institutions participating in cooperative research projects can use for IRB review:

> Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a ***joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.***

Dr. Bartlett explained the differences between joint review arrangements (i.e., several IRBs develop an agreement about respective areas of responsibility, and the direct awardee lists each of the local IRBs on its FWA); relying on the review of another qualified IRB (i.e., several research institutions rely on a central IRB, either from one of the institutions, a commercial IRB, or an IRB created specifically for the study); and similar arrangements for avoiding duplication of effort. He noted that one or more of these models is potentially workable in a given cooperative research effort, depending on the specifics of the research protocol, the expertise and resources available to the IRBs, the prior working relationships among the IRBs, the requirement to comply with local laws and regulations, and the total number of performance sites.

In November 2005 and November 2006, the Office for Human Research Protections (OHRP) in the U.S. Department of Health and Human Services (HHS) cosponsored meetings with the National Institutes of Health (NIH), the Association of American Medical Colleges, and the American Society of Clinical Oncology on alternative IRB models. A key conclusion of those meetings was that despite the existing flexibility in federal regulations, some institutions are reluctant to designate external IRBs for cooperative research. (Summaries of both meetings were included under Tab #12 in Committee members' briefing books.)

One major reason that research institutions are reluctant to designate external IRBs is that OHRP holds an institution engaged in human subjects research accountable for noncompliance on the part of an external IRB designated on its Federal wide Assurance (FWA). Thus, research institutions worry that if an external IRB makes a mistake, they (rather than the external IRB) may be held liable. This is a reasonable concern. To address this problem, OHRP is considering changing federal regulations (45 CFR 46) to enable OHRP to hold external IRBs accountable for compliance. A request for information (RFI) on this topic is now under development. The RFI will delineate various types of responsibilities and who should be held responsible for them:

- Some responsibilities may be specific to the IRB (e.g., altering or waiving informed consent).
- Some responsibilities may be specific to the research institutions (e.g., communicating the expectation to investigators to get IRB approval before research, making sure no investigators do research without informed consent unless a waiver has been approved by the IRB).
- Some responsibilities may be the responsibility of either the IRB or research institutions (e.g., determining the applicability of 45 CFR 46, fulfilling documentation and record-keeping requirements).

The RFI will also investigate whether some responsibilities may be shared by the IRB and the research institution.

Questions & Comments

Dr. Nicola Longo, speaking from the audience, noted that getting multiple IRBs' approval for research at more than one site—or just to establish disease registries to follow patients with rare disorders just to get the natural history of the disease—has been challenging and poses a major obstacle to clinical research on rare disorders. He asked whether there might be some kind of a central IRB that would review research on rare disorders. Dr. Bartlett responded that a central IRB for such research might very well be possible. The National Cancer Institute (NCI) has established its own IRB, which reviews all the cooperative research, and there is no reason that, for example, the National Institute of Child Health and Human Development (NICHD) could not establish its own IRB.

Ms. Terry observed that many people think IRBs worry about the legal liability of protocols, are risk averse, and primarily want to protect institutions from liability. If that is true, could modifying the Common Rule to hold IRBs accountable make IRBs become more risk averse? Dr. Bartlett said her point is well taken, because the organization that makes the mistake would be held accountable. Dr. Susan Berry, speaking from the audience, asked whether there is a role for the Accreditation of Human Research Protection Programs Inc., an organization that accredits IRBs and other human subject protection systems. Dr. Bartlett replied that there probably is. Dr. Fleischman noted that that IRBs tend to worry more about regulatory liability (i.e., that OHRP will come in and shut down the institution's research) than about legal liability.

C. Translational Research in the Context of Newborn Screening: How Can We Make It Work?

Alan R. Fleischman, M.D.
Senior Vice President and Medical Director
March of Dimes Birth Defects Foundation
Committee Representative

Dr. Fleischman explained that gaining approval for multicenter research related to newborn screening in the context of the protection of human subjects of research can be very challenging. The job of IRBs is to protect human subjects, and IRBs are quite protective, as they should be. Local IRBs are supposed to ensure local understanding, but most research today is not local, and local IRBs can be an impediment to research. IRBs rarely facilitate research; what they do is ensure institutions' compliance with federal and state regulations and laws and try to protect institutions. If there is no grievance process for an IRB's decision, an IRB's rejection leaves research institutions with no recourse. Central IRBs may help, but even if NICHD were to establish its own IRB, local IRBs would be free to accept or reject its decisions. The real answer to making translational research work in the context of newborn screening is doing a lot of preparation and helping IRBs to think through their analysis. Most lawyers say, "Do not go to an IRB with a research proposal until you are very well prepared."

Two States' Approaches to Newborn Screening Research. Dr. Fleischman described different approaches to the protection of human subjects in newborn screening pilot studies used by Massachusetts and California:

- **Massachusetts Oral Consent.** Massachusetts has taken the position that screening for conditions to obtain new and generalizable scientific knowledge without evidence-based proof of benefit to the child screened constitutes research—and is therefore not exempt from IRB review. In 1999, Massachusetts wanted to do two pilot newborn screening studies, one in which

newborns would be screened for cystic fibrosis and one in which newborns would be screened for 19 additional disorders, to justify the expansion of newborn screening beyond the 10 disorders included in routine newborn screening. Two IRBs reviewed the pilot screening studies and decided that although parental consent for their children's participation in the studies should be required, the requirement for written consent from parents could be waived. A brochure explaining the optional newborn screening for the 20 additional disorders was distributed to parents of newborns in Massachusetts, and parents' oral consent was documented on a form by a nurse, using an X in a box to indicate that parents had declined to provide their consent. This consent protocol worked extremely well. Few families declined to participate in the pilot screening studies. The pilot study of screening for severe combined immunodeficiency (SCID) in Massachusetts is using the same protocol for obtaining parents' consent to their newborns' participation. (In 1987, Massachusetts also did HIV prevalence testing in child-bearing women by measuring maternal antibodies in deidentfied residual newborn blood spots. They argued that this was a prevalence survey using anonymous, deidentified information, not human subjects research and therefore exempt from IRB review.)

- **California Written Consent.** In 2000, the California legislature mandated pilot testing of tandem mass spectrometry (MS/MS) that could potentially use the same blood spot specimen collected during routine newborn screening to screen for more than 29 additional metabolic disorders. Rather than running the MS/MS analysis on all of newborn specimens without parental consent, California decided to require written parental consent to MS/MS pilot testing on their children. A pilot study of MS/MS screening in California begun in 2002 with the goal of screening 400,000 newborns in 1 year. Because of logistical problems encountered by hospitals in obtaining consent in the study, informed consent was obtained for only 47 percent of newborns during the study period, and there were missed cases. Feuchtbaum et al., in a 2007 article on this experience published in the *Journal of Empirical Research on Human Research Ethics*, concluded that "the legitimate needs of society in this situation should not be sacrificed to the autonomy interests of the few parents who did not want their infant to participate in the study" and that "in the future, parental consent should be waived."

Questions To Consider Before Going to an IRB with Research. Before going to an IRB with a research proposal related to newborn screening, treatment, or followup, researchers, clinical provider networks, translational research networks should review the relevant federal regulations and prepare to answer the following questions:

1. **Is the study research?** Research seeks generalizable knowledge. It is important to distinguish research from surveillance, quality improvement, and clinical care.
2. **Does the study involve human subjects?** OHRP considers private information or specimens to be deidentified when they cannot be linked to specific individuals. The devil is in the details. If an researcher has your blood, that person knows a lot about you, but if the researcher promises not to try to find out who you are and is held accountable, then it is highly unlikely that the researcher will identify you. If there is a process where a researcher who is getting deidentified samples promises not seek reidentification in any way and is separated by a firewall from identified information, then those are deidentified samples and the study is not human subjects research.
3. **Is the study exempt from IRB review?** Public data sets, existing deidentified data specimens, and studies of public benefit and service programs are exempt from IRB, and it is important to keep these things in mind.

4. **Does the study require consent? Can consent be waived? Is oral consent justifiable?** Dr. Botkin noted that the Common Rule allows for a waiver or alteration of informed consent if four criteria are met (45 CFR 46.116d). It is important to understand when consent can be waived before going to an IRB, so you are able to include language to justify a waiver (e.g., "could not practicably be carried out" for most population studies, and study is of minimal risk and will not adversely affect the rights and welfare of the subjects).
5. **How many institutions will be involved? Will there be multiple individual reviews, joint review arrangements, or cooperative reviews?** Dr. Fleischman described the different approaches to gaining IRB approval used by the Children's Oncology Group at NCI and the National Children's Study:
    - The Children's Oncology Group has engaged every children's hospital and major oncology program in the United States. Because all children's oncology research in the United States is centralized, 85 percent of children with cancer are in clinical trials, something that has been incredibly helpful. Even when people cede the review of the research to a central IRB, they remain locally responsible for the "local context." Many fine hospitals have not ceded control to a central IRB; they have their own IRB, which does not want to lose resources, and they like it.
    - The National Children's Study, on which Dr. Fleischman is working with Dr. Alexander from NICHD, is now in the field in two pilot sites, Queens, New York, and North Carolina. About 3 years ago, the National Children's Study planners created a Human Subject Workgroup with the chairs of all the IRBs that would be involved in the study to think about problems prospectively and how to address them before the study was submitted for their review. This approach was very helpful. In Queens, the many participating hospitals have ceded authority to the Mount Sinai Medical Center IRB in cooperative agreements—an approach that seems to be working. In North Carolina, the larger hospital decided that it did not want the smaller hospitals to cede authority to the larger institution's IRB (for reasons that are not yet clear), so a different approach has been used.

Questions & Comments

Dr. Chen asked Dr. Fleischman to comment on the effort Dr. Bartlett described by the Office for Human Research Protections (OHRP) to define lines of responsibility for different IRBs and institutions. Dr. Fleischman replied that this is a well-intentioned effort by OHRP to try to help, but he does not think that it will change IRBs worried about more about regulatory liability (i.e., that OHRP will come in and shut down the institution's research).

Dr. Watson asked how to balance the IRB issues in the Newborn Screening Translational Research Network (NBSTRN), noting that there are widely distributed patients in 100 metabolic centers around the country, who are going to be more comfortable entering into a large data collection activity if it is done through their own doctor than through the Rare Disease Clinical Consortium (with about 12 centers and about 20 percent of patients with rare diseases, which is inadequate). Dr. Botkin replied that it is relatively easy to sign up individual practitioners and involves a site review and Federal wide Assurance (FWA) signature. The less efficient part is trying to sign up an institution that has a preexisting IRB that wants to have some oversight responsibility.

Dr. Boyle noted that the study of the value of routine second specimens that the Committee has been trying to move forward has faced significant challenges from IRBs and that that was the impetus for this panel. States vary in whether they view the study as research or as public health practice or program evaluation that is not human subjects research. She believes it is the latter and asked for guidance about this, saying she heard the panelists saying that it is important to equip state programs to make a better case that this study is not human subjects research.

Dr. Fleischman recommended inviting commissioners of health and the chairs of their IRBs to a meeting to discuss the routine second specimen study referred to by Dr. Boyle. He suggested presenting these individuals with the idea of an anonymized population-based, public health practice surveillance program at the meeting to develop a better understanding of what their concerns are and try to address them. If the routine second specimen study is not anonymized, it is research, and it will be necessary to engage IRBs to hear what their problems are. Dr. Bartlett, who served as a member of an IRB, agreed with Dr. Fleischman about the importance of understanding the lingo and establishing lines of communication with IRBs in advance, especially for studies that are more public health types of protocols, which are different from many of the typical protocols seen by IRBs. Dr. Botkin added that it is important that whoever puts the protocol together have a good understanding of the regulations and make a pitch for how they think the study should be approved. He also recommended talking with people at OHRP. If OHRP gives clear guidance, that will relieve IRBs' concerns about legal liability.

Dr. Kus asked the panelists to expand on oral consent and its viability for pilot studies in newborn screening. Dr. Bartlett said that oral consent decisions by local IRBs mean there is one of two things: (1) a waiver of the regulatory requirement for informed consent; or (2) a waiver of the requirement for documentation of the informed consent (see CFR Title V, Part 46, Subpart A, §46.117 for criteria to permit this). A waiver of the regulatory requirement for informed consent does not preclude the provision of an information sheet or providing an oral explanation.

Dr. Howell asked whether the panelists had any information about well-functioning IRBs in the public health sector. Dr. Calonge said the public health department in Colorado is engaged in public health research and has a very active IRB, but he suspects there is variation from state to state. The local health departments would like to use the Colorado public health department's IRB, but there are insufficient resources for the IRB to take on that role because the Colorado legislature does not think of the public health department as performing research.

Ms. Terry asked the implications for population-based newborn screening research are of the decision by NIH, after a paper last fall talked about identifiability even in small amounts of DNA in pools, to move its Genetic Association Information Network (GAIN) data behind a firewall, although the GAIN data had previously considered deidentified and were in front of the firewall. Dr. Bartlett said that NIH came to OHRP to discuss that study, and in his view, the information is not "readily identifiable."

Dr. Anne Comeau, speaking from the audience, gave support to the idea of bringing IRB people together. When Massachusetts did the pilot newborn screening studies in which it obtained parents' oral consent, they held meetings for the 55 hospital CEOs and IRB chairs in advance to educate them about what they were going to do. Local IRBs could make the protocol more stringent, but some IRBs that did that got sued because had made it so complex. She also noted that it is important to realize that there is consent for consent's sake and consent for education. As a parent, she would rather know she is participating in research in advance rather than get a call out of the blue about research.

Dr. Nancy Green, speaking from the audience, said that if a research protocol gets bounced back by an IRB, it is too late and identified another resource for the Newborn Screening Translational Research Networks (NBSTRN). The Clinical Translational Research Centers funded by the National Center for Research Resources at NIH at 30+ institutions are quickly expanding, and within the pediatric part of this network there is an IRB consultation services, chaired by Alex Kahn at University of California. Dr. Mei Baker, also speaking from the audience, suggested that another model might be Wisconsin's Institute for Translation Research.

VIII. RESIDUAL SPECIMENS FROM NEWBORN SCREENING: POLICIES GOVERNING STORAGE, RETENTION, AND USES

Procedures and polices for the management of the approximately 4 million residual dried blood spots that remain each year after being collected during newborn screening vary widely from state to state. In this session, there were two presentations on residual specimens from newborn screening:

- A presentation on the history of efforts to improve state policies on the retention, storage, and use of dried blood spot specimens collected during newborn screening and recent controversies related to these matters by Dr. Harry Hannon
- A proposal for addressing ethical and regulatory issues in the use of specimens from newborn screening, given that most newborn screening programs do not require consent for screening, by Dr. Jeffrey Botkin

A. Storage, Retention, and Use of Residual Dried Blood Spots From Newborn Screening

William H. Hannon, Ph.D.
Chief, Biochemical Branch
Division of Laboratory Sciences
National Center for Environmental Health
Centers for Disease Control and Prevention (CDC)

Dr. Hannon explained that there is a large move by states toward indefinite storage of residual dried blood spots from newborn screening. The reasons for retaining these residual specimens include the following: (1) legal accountability (e.g., existence of a sample and its adequate collection); (2) future DNA testing; (3) reconfirmation of newborn screening analytical results; (4) new method evaluations and comparisons; (5) epidemiological or other public health surveys (e.g., to determine HIV seroprevalence); (6) special health-related studies for patient or family; (7) forensic studies; (8) confirmatory diagnosis (reconfirm false negative or false positive finding); (9) quality assurance and public health needs; (10) research uses (DNA extraction—understanding disease history; gene-environment interactions); (11) clinical testing (e.g., post mortem identification of disease cause); and (12) nonmedical uses (e.g., identification of kidnapped children, deceased persons, paternity).

State policies addressing the retention, storage, and use of residual dried blood spots are widely varying, and several people and entities have issued guidelines and called for their improvement:

- In 1996, the Council of Regional Networks for Genetic Services (CORN) issued guidelines addressing the retention, storage, and use of residual dried blood spots (Therrell, Hannon, et al., *Biochemical and Molecular Medicine* 57:116-124, 1996).

- In 2000, an American Academy of Pediatrics (AAP) report from the Newborn Screening Task Force spoke of the need to develop policies for linked and unlinked residual samples, organize collaborative efforts to develop minimum standards for storage of residual samples at the state level, consider creating a national or multistate population-based specimen resource for research (*Pediatrics*, 106 Suppl, 2000).
- In 2005, the Association of Public Health Laboratories (APHL) issued a position/policy statement on residual newborn screening specimens saying that there may be reasons other than quality assurance to save dried blood spot specimens and calling for clear guidelines on retaining residual specimens that are incorporated into national consensus policies that state health departments follow (http://www.aphl.org).

To date, however, little action has been taken to implement these recommendations. The lack of transparency in policies governing the retention, storage, and use of residual specimens from newborn screening is feeding media and public controversies. Members of the public are not aware of retention and use of dried blood spots, and several recent articles have aroused concerns about the use of residual dried blood spots without individual consent. Public participation and consent to the retention and use of residual dried blood spots is essential. The CORN report discussed this in 1996.

In 2003, the Centers for Disease Control and Prevention (CDC) gave the following information about states' practices with respect to the storage, retention, and use of residual dried blood spots:

- There was great variability from state to state in the duration of residual dried blood spot storage and adherence to suggested storage guidelines.
- Just 45 percent of states had written guideline concerning the uses of their residual samples.
- Just 16 percent of states informed parents that they retained residual dried blood spots (and the notification was often just a sentence saying that the parents might be contacted later)
- Nearly 80 percent of states favored future storage of identifiable samples at the state level.
- When states were asked where they would prefer to store residual newborn screening specimens, assuming funding were available, most of them responded that they would prefer to store them in a state facility rather than a regional or national facility.

Participants at the CDC meeting agreed that it would be possible to create a virtual repository of specimens for research, notwithstanding several challenges, and identified several steps in a strategic plan for developing a virtual database of available specimens for research use: (1) create a working group to develop and publish a strategic plan for implementation; (2) establish a central gatekeeper (to get public trust); (3) establish criteria for inclusion, access, and use; (4) develop consensus standards for storage, quality assurance, and cataloging/retrieval, data elements, linkages to facilitate finding specimens; (5) plan pilot studies to demonstrate usefulness (there are enough); (6) address gaps and feasibility issues; and (6) hold a larger stakeholders meeting to get buy-in.

Dr. Hannon closed his presentation with several thoughts. There is still a need to develop state policies on the retention, storage, and use of residual specimens from newborn screening. The policies exist but they are not used, and what is needed at this point is stakeholder buy-in. The National Institutes of Health (NIH) is funding the Newborn Screening Translational Research Network with long-term outcomes for rare conditions diagnosed via newborn screening, and a virtual specimen database for use in conjunction with the NBSTRN database is possible. States appear interested in collaborating. Finally,

there is a tendency in the states that refer to these original specimens as patient "records' for policy implementation. It is time to move from talk to action.

Questions & Comments

Dr. Buckley asked how many states get consent from parents when they obtain dried blood spots from newborns. Dr. Brad Therrell, speaking from the audience said that three jurisdictions (Wyoming, the District of Columbia, and Maryland) get consent. Dr. Buckley suggested that the Advisory Committee consider recommending that all states get consent from the family—and giving them the choice of opting out if they want to—to have newborn screening and/or to have residual specimens retained for future study.

B. Research Using Residual Specimens: Ethical and Regulatory Considerations

Jeffrey R. Botkin, M.D., M.P.H.
Associate Professor of Pediatrics and Medical Ethics
Department of Pediatrics
University of Utah School of Medicine

Dr. Botkin discussed the use of residual dried blood spots from newborn screening in research and suggested that a community consent model should replace the individual consent model for addressing ethical and regulatory issues in the use of specimens from newborn screening. At the outset, he presented the following definitions:

- *Identifiable specimens* are specimens whose tissue source can be identified by somebody and include linked or coded specimens for which someone has the key.
- *Deidentified specimens* are "anonymized" specimens whose source cannot be identified. This definition is more stringent than the definition in 45 CFR 46 ("not readily identifiable by the investigator") and in the Health Insurance Portability and Accountability Act (which requires the removal of 18 specified potential identifiers for a specimen to be considered deidentified).

Depending on the nature of their study, Dr. Botkin noted, researchers have an option of using either anonymized specimens or linked (identifiable) specimens. Anonymized and linked specimens have different pros and cons.

- Anonymized specimens
    - Pros: Anonymized specimens are valuable for epidemiologic research. Research using anonymized specimens does not involve "human subjects" under U.S. regulations. Such research requires minimal review by institutional review boards (IRBs). An IRB defines exempt research and may review the deidentification process. No consent usually necessary for anonymous use of anonymized specimens (however, consent may be appropriate for collection and storage of the specimens to begin with).
    - Cons: It is impossible to link anonymized specimens with health outcomes of specific individuals. It is impossible to contact the family with beneficial health information.
- Linked (identifiable) specimens
    - Pros: Health tracking is possible. The return of health information is possible.

- Cons: IRB review oversight of research is necessary. Informed permission may be necessary (making it difficult to use existing samples). The return of information may pose a risk to children and/or their families (may not always be beneficial if information is inaccurate or misinterpreted).

Dr. Botkin said he disagrees with 2004 Office for Human Research Protections (OHRP) guidance that Investigator B, who obtains tissue specimens from Investigator A, who obtained tissues in the conduct of research and banked them with identifiers, is not conducting human subject research if he/she signs an agreement not to seek the identities of tissue sources (htttp://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf). He does not believe that OHRP's guidance accurately interprets what federal rules say, may not prevent information getting back to patients about research for which they did not give consent, and does not specify who will oversee these arrangements, make sure that they are properly drafted, stored, reviewed, etc.

Because only two states and the District of Columbia have a process for obtaining informed permission from parents for newborn screening, most states have no infrastructure to obtain parents' permission for newborn screening. Moreover, public health and nursery personnel oppose seeking permission. Important questions therefore are: Should permission be obtained from parents to retain their child's residual dried blood spot for research? Should permission be obtained from parents to use their child's residual dried blood spot in research? Would such permission be for research specific to newborn screening conditions or for other research as well?

In August 2000, the American Academy of Pediatrics (AAP) and the Health Resources and Services Administration published a report from the Newborn Screening Task Force with recommendations about the policies governing the use of unlinked residual specimens (*Pediatrics,* 106 Suppl, 2000). That report said that for the use of identifiable newborn screening samples in research, both IRB approval and parental permission should be obtained.

Dr. Botkin believes that an individual consent requirement and process in newborn screening undermine the public health approach to newborn screening. Noting that people are increasingly doing research using large databases and large sets of tissue repositories to look at population issues, He proposed using a deliberative democratic process to provide "community consent" as an alternative to individual informed consent. This would give people a more robust understanding of what the issues are with the retention and use of samples. Currently, Dr. Botkin is working on a project related to this with funding from the National Human Genome Research Institute to develop the theoretical foundation for methods for promoting public dialogue on the use of residual newborn screening samples. He believes that it will disastrous if the public is not more effectively and thoroughly engaged.

Questions & Comments

Ms. Terry said she totally agreed that the public needs consultation. The Genetic Alliance is worried there is no public voice and trying to do rectify that situation. She recommended that Dr. Botkin talk to the Genetics and Public Policy Center about their work on biobanking.

IX. COMMITTEE BUSINESS—SUBCOMMITTEE REPORTS & DISCUSSION

The Advisory Committee's Laboratory Standards & Procedures Subcommittee, Education & Training Subcommittee, and Followup & Treatment Subcommittee held meetings that were open to the public during the morning of February 26, 2008. On February 27th, the subcommittee chairs gave a report to the full Committee, as discussed below.

A. Laboratory Standards & Procedures Subcommittee Report

Gerard Vockley, M.D., Ph.D.
Chief of Medical Genetics
Children's Hospital of Pittsburgh of UPMC
Professor of Human Genetics and Pediatrics
University of Pittsburgh
Committee Member

Dr. Vockley the chair of the Laboratory Standards & Procedures Subcommittee, reported that the subcommittee had received several updates at its February 26th meeting:

- Dr. Harry Hannon gave a progress report on the study of routine second screens for congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH) that was begun by the National Newborn Screening and Genetic Resource Center and Association of Public Health Laboratories on behalf of the subcommittee some time ago. The problems in getting state-specific institutional review board (IRB) approvals finally seem to be resolving, and enrollment in the study is nearing the level needed. There should be something to report later this year.
- Dr. Rinaldo reported that the Region 4 study on tandem mass spectrometry (MS/MS) screening standards is continuing to develop its very robust newborn screening database that allows different states to compare their laboratory results with those of other states and use that information in feedback to improve what they are doing. Dr. Rinaldo would like to involve clinician users who are dealing with newborns as well as labs doing newborn screening. Dr. Vockley is going to look at the database to consider how clinicians might be involved.

The subcommittee also discussed some technologies that it might be seeing in the coming meetings. Many of the proposals that the subcommittee has had and that are potentially coming forward are for lysosomal storage disorders. Dr. Bob Vogt from the Centers for Disease Control and Prevention (CDC) talked about efforts to advance screening for lysosomal storage disorders. Genzyme has agreed to provide synthesized substrates for Pompe, Fabry, Gaucher, Krabbe, and Nieman-Pick disease, and others. CDC is standardizing an MS/MS test for several lysosomal disorders and will distribute substrates. The Mayo Clinic is going to compare an antigen-based test (multiplexable) and MS/MS. There should be some results by October 2009.

Finally, Dr. Mike Watson gave the subcommittee a report on the Newborn Screening Translational Research Network (NBSTRN) similar to the one he gave the full Committee. The subcommittee was interested in how technologies for screening might impact that. The consensus was that it is too early to know.

B. Education & Training Subcommittee Report

Tracy L. Trotter, M.D., F.A.A.P.
Senior Partner
Pediatric and Adolescent Medicine
San Ramon Valley Primary Care Medical Group
Committee Member

Dr. Trotter, who chairs the Education & Training Subcommittee with Jana Monaco, reported that the subcommittee had received several updates at its February 26th meeting:

- The National Newborn Screening and Genetics Resource Center reported that the Genetic Education Materials (GEM) database is back up and links are being reestablished.
- Joyce Hooker, from the Mountain States Genetics Regional Collaborative, reported that there are 50+ education and training programs at the seven HRSA-funded Regional Genetics and Newborn Screening Collaboratives. The subcommittee will review these and consider how such programs might be developed and used most efficiently.
- The Genetic Alliance reported that it had surveyed the 12 voting members of the Advisory Committee with respect to the Advisory Committee's level of emphasis on genetics education and training. Five members agreed, four were neutral, and three disagreed with the following statement: "Genomic education is a high priority."

The Education & Training Subcommittee also continued discussing how to improve primary care physicians' knowledge about genetics and newborn screening. A 2008 article in *Pediatrics* indicated that newborn screening poses challenges for primary care physicians, both educationally and in the management of affected infants *(Pediatrics* 2008: 121; 192-217). Although 70 to 80 percent of patients have confidence in their primary care providers' ability to provide information about genetic disorders and tests, 60 percent of primary care providers feel they are not qualified to recommend, order, or interpret genetic tests.

To educate primary care physicians about genetics and newborn screening, the Education & Training Subcommittee is partnering with the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetricians and Gynecologists (ACOG). The focus will include education regarding primary care physicians' response to an out-of-range screening result (ACT sheets/state newborn screening programs), their coordination of a complete evaluation of an affected infant, their provision of a medical home and coordination of care for affected children, and their role in educating families and health care workers.

The subcommittee is also planning to serve in an advisory capacity to current groups involved in educating primary care physicians and public/family education: National Human Genome Research Institute, the National Newborn Screening and Genetics Resource Center, Genetic Alliance, National Coordinating Center for the HRSA-funded Regional Genetics and Newborn Screening Collaborative

Groups, the National Coalition for Health Professional Education in Genetics, professional medical associations, and others.

In June 2009, the National Human Genome Research Institute is holding a meeting called "Developing a Blueprint for Primary Care Physician Education in Genomic Education." Dr. Trotter reported that the Education & Training Subcommittee would like to add a 2-hour maternal and child health roundtable to the meeting and requested the Advisory Committee's approval.

Questions & Comments

Dr. Dougherty suggested that the Education & Training Subcommittee work with the Quality Improvement Network at AAP, noting that they now have a senior medical officer for the quality cabinet.

Dr. Howell and other Advisory Committee members agreed that tapping in to the June 2009 National Human Genome Research Institute would be a good idea, and the Committee unanimously adopted the following motion.

- **MOTION #3 (APPROVED): The Advisory Committee approves the Education & Training Subcommittee's request to add a 2-hour maternal and child health roundtable to the National Human Genome Research Institute's June 2009 meeting "Developing a Blueprint for Primary Care Physician Education in Genomic Education."**

Dr. Howell indicated that the Education & Training Subcommittee chair Dr. Trotter would be in charge of ensuring that the maternal and child health roundtable was added to the June 2009 meeting.

C. Followup & Treatment Subcommittee Report

Colleen Boyle, Ph.D., M.S.
Director, Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention (CDC)

Dr. Boyle, the chair of the Followup & Treatment Subcommittee, reported that the subcommittee had been reconstituted and now has several new members: Dr. Celia Kaye, Dr. Susan Berry, Dr. James Figge, Dr. Carl Cooley, and Dr. Fred Lorey. Dr. Alan Hinman and Jill Fisch will continue to serve. Dr. Dougherty, Dr. Kus, and Dr. Watson will continue to serve as representatives from the Advisory Committee. Dr. Brad Therrell and Dr. Alex Kemper will serve as consultants. Jill Shuger will continue as the liaison from HRSA's Maternal and Child Health Services Bureau.

Update on the Subcommittee's Ongoing Activities. The Followup & Treatment Subcommittee is continuing its efforts to (1) define and characterize long-term followup care after newborn screening; and (2) examine issues related to insurance coverage of medical foods.

- **Long-term followup of newborns with conditions detected via newborn screening**. The Followup & Treatment Subcommittee is developing a second article on long-term followup in

newborn screening for publication in *Genetics in Medicine*. The first article by Dr. Alex Kemper outlined the major components of long-term followup in newborn screening. The sequel being planned will outline the roles and responsibilities of major players in long-term followup (namely, affected individuals/families, primary care providers, specialty and subspecialty providers, and public health agencies).

- **Insurance coverage of medical foods for individuals with metabolic conditions identified via newborn screening**. In June 2008, the Followup & Treatment Subcommittee held a meeting of experts in the public and private worlds to discuss insurance coverage for medical foods and prescribed solid modified foods for the treatment of inborn errors of metabolism identified via newborn screening. The subcommittee drafted a letter to be sent from the Advisory Committee to the HHS Secretary recommending a number of legislative and policy measures to ensure that families get insurance coverage for such foods. The subcommittee made changes to the letter on February 26, 2009, and Dr. Boyle believes it is stronger now. The subcommittee is doing a survey of affected families with the help of the New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services, the Southeastern Regional Genetics Group, and the Region 4 Genetics Collaborative. Full implementation of the survey is expected in March 2009.

Subcommittee's Preliminary Discussion of Data Needed To Ensure Optimal Long-Term Followup After Newborn Screening. The main item on the agenda for the Followup & Treatment Subcommittee's meeting on February 26, 2009, was to begin developing a consensus on a set of variables for the electronic exchange of information needed to ensure optimal long-term followup of infants with conditions detected via newborn screening. It was agreed that variables should pertain to the four components of long-term followup identified by the Followup & Treatment Subcommittee: (1) care coordination through a medical home, (2) evidence-based treatment, (3) continuous quality improvement, and (4) new knowledge discovery. In addition, the variables should address the information needs of the key participants in long-term followup: health care providers, consumers, and public health entities.

As background, the subcommittee heard several presentations. First, Dr. Greg Downing, from the HHS Office of the Secretary, gave an overview of progress toward the development and use of interoperable health information technology at the macro level, as well as the potential of such technology in newborn screening, confirmatory testing, diagnosis, treatment, and followup in the United States. Second, grantees undertaking complementary activities for developing data systems and activities for long-term followup after newborn screening with support from the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), and National Institutes of Health (NIH) gave presentations to help subcommittee members understand the purpose of long-term followup data and data needs from the perspective of three different funding agencies.

After the presentations, Dr. Hinman led meeting attendees in a discussion. The discussion quickly turned from developing a set of variables for the electronic exchange of information needed to ensure optimal long-term followup of infants with conditions detected via newborn screening to how should the subcommittee go about developing such a data set. Issues that arose in this context are the need to harmonize case definitions, the need to figure out what the critical question that need to be answered with respect to long-term followup, and the need to standardize data categories and think about what levels of information to include in each category.

There was some uncertainty about what the next steps with respect to the Followup & Treatment Subcommittee's development of a set of variables for the electronic exchange of information needed to ensure optimal long-term followup should be. Finally, it was decided that the subcommittee would discuss next steps at its next monthly phone call. The next steps will probably include defining what the critical questions are, defining the minimum data set, identifying areas where the lack of standards poses a problem (e.g., the lack of a standard case definition). Another possibility might be to explore the development of a use for long-term followup in newborn screening in conjunction with the Quality Use Case to complement the newborn screening use case published by the HHS Office of the National Coordinator for Health Information Technology. Finally, the subcommittee will have to consider what its role is as opposed to that of various federal agencies addressing long-term followup in newborn screening.

X. PUBLIC COMMENTS/COMMITTEE CORRESPONDENCE

Dr. Howell said there would be no additional public comments beyond those related to the SCID nomination that had been presented earlier in the meeting (full text included in Appendix A). He urged Advisory Committee members to read three letters to the Advisory Committee that were included under Tab #5 in their briefing materials:

- A letter from Jacque Waggoner, on behalf of Hunter's Hope Foundation, commending the Advisory Committee for its work on Krabbe disease and recommending a video from the parents of a little boy with Krabbe disease (Judson Levasheff) who was diagnosed too late to receive treatment and died when he was 2 years old (http://www.storyofjudson.com/meetjudson).
- A letter from Dawn Lobell, the mother of a child with a metabolic disorder included in the uniform newborn screening panel, to express her support of mandatory screening for all newborns and expressing concerns about the Maryland Department of Health and Mental Hygiene's efforts to defeat a newborn screening bill in the state legislature that would have required Maryland to adopt the two-tiered screening system used in Massachusetts and eliminated the current ability of parents to refuse newborn screening (Senate Bill 160 in the Senate and HB 180 in the House).
- A letter from Richard Kelly, M.D., Ph.D., at the Kennedy Krieger Institute expressing concerns about tactics used to oppose changes in newborn screening in Maryland.

Dr. Howell stated that the Committee would want to address the issues raised with respect to problems encountered in efforts to reform newborn screening in Maryland in the future.

XI. COMMITTEE BUSINESS

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
Professor, Department of Pediatrics
Leonard M. Miller School of Medicine
University of Miami

In the final session of the meeting, the Committee finished up some business it had begun earlier:

a. Approval of the proposed letter from the Advisory Committee to the HHS Secretary on reimbursement for medical foods

b. Approval of a change proposed by Dr. Calonge to the Decision Criteria & Process Workgroup's report

c. Discussion of the Committee's letter regarding gaps in the evidence for severe combined immunodeficiency disorder (SCID)

d. Approval of changes to the Advisory Committee's operating procedures ("ACHDNC: Policies and Procedures for the Operation and the Development of Recommendations for Screening Newborns and Children for Heritable Disorders and for the Heritable Disorders Program") made to conform with the Advisory Committee's new charter.

e. Planning for the Advisory Committee's May and September 2009 meetings

f. Other business

A. Approval of the Committee's Letter on Medical Foods to the HHS Secretary—Dr. Boyle

The chair of the Followup & Treatment Subcommittee Dr. Boyle presented a slightly revised version of the letter from the Committee to the HHS Secretary on medical foods. Dr. Lloyd-Puryear suggested the following change: In the last recommendation, after Medicaid coverage, add the words Children's Health Insurance Program (CHIP). Dr. Boyle agreed to make this change. Dr. Lloyd-Puryear stated that several enclosures should be included with the letter (i.e., the recommended uniform newborn screening panel from the Committee, a list of medical foods that are required for those conditions, and references to justify these medical foods).

Finally, Dr. Trotter proposed and Ms. Monaco seconded the following motion, which the Committee voted to approve unanimously.

- **MOTION #4 (APPROVED): Send the newly revised letter from the Advisory Committee recommending legislative and policy changes to ensure coverage of medical foods (and related attachments) to the HHS Secretary.**

B. Change to the Decision Criteria & Process Workgroup's Report—Dr. Calonge

Dr. Calonge, the chair of the Advisory Committee's Decision Criteria & Process Workgroup, proposed a slight modification to the report and framework approved by the Committee the previous day. Committee members had raised questions about the need to include Key Question #1 (Is there *direct evidence* that screening for the condition at birth leads to improved health outcomes for the infant or child to be screened, or for the child's family?) in the decision framework proposed by the Decision Criteria & Process Workgroup report, if the answer to the question would always be "No."

Dr. Calonge said he had gone back to the defintion of direct evidence. He reported that the U.S. Preventive Services Task Force (USPTF) defines direct evidence as evidence that exists when an intervention and outcomes are measured in the same body of evidence. A randomized clinic trial (RCT) provides direct evidence of the highest quality, and the USPTF would not consider approving something without that; however, an observational study or population-based screening (e.g., before screening for a condition, there were X deaths from the condition; then after screening, there were no deaths) can provide direct evidence of lower quality than that from an RCT. This means that there could be a "Yes" answer to Key Question #1 even in the absence of an RCT.

Dr. Calonge made and Dr. Rinaldo seconded the following motion, which the Committee passed unanimously:

- **MOTION #5 (APPROVED): In the Decision & Process Criteria Workgroup's report, make it clear in Key Question #1 that direct evidence is a single body of evidence that establishes a connection between an intervention and health outcomes. Thus, although the highest quality direct evidence is from randomized clinical trials (RCTs), direct evidence of lesser quality may come from other types of studies.**

C. Discussion of the Committee's Letter Regarding Gaps in the Evidence for SCID—Dr. Vockley

Dr. Vockley, who at Dr. Howell's request had convened a small group to propose what the Advisory Committee should tell the nominators of SCID about the gaps remaining in the evidence for SCID that must be filled before the Committee could recommend SCID's inclusion on the uniform newborn screening panel, proposed that the Advisory Committee inform the nominators of SCID that the following conditions must be met before the Advisory Committee would vote to include SCID on the uniform newborn screening panel:

1. Prospective identification of at least one confirmed case of SCID through newborn screening.
2. Continued false positive rate of < 0.1% . [Dr. Vockley said the Wisconsin SCID screening program is doing well better than this, so this should not be a barrier.]
3. Willingness of another state screening lab to implement SCID screening. [Dr. Vockley said Wisconsin is piloting SCID screening, and Massachusetts has started; and Texas is going to partner with Massachusetts to pilot SCID screening on a small scale.]

4. Quality control materials from the CDC by June 2009. [Dr. Vockley said Dr. Bob Vogt has committed CDC to make something available by June 2009.]
5. Appropriate resources available to fund above [Dr. Vockley said this is not really an information gap, just a recommendation to policymakers to provide resources to help achieve the conditions noted above.]

Questions & Comments

At Dr. Calonge's suggestion, Dr. Vockley agreed to make the title of the list to "Gaps Identified in the Evidence" rather than "Conditions To Be Met."

Dr. Kelm and Ms. Terry cautioned the Committee to bear in mind that whatever bar is set for SCID may be considered a precedent—and therefore not to set the bar higher for SCID than for other conditions. Dr. Vockley explained that the Committee was not setting a bar; it was just identifying information needed for SCID.

Ms. Terry and others said that it was not clear who was responsible for each of the specific points in the list. Dr. Howell noted that activities related to most of the points is already underway and that at some point, a screening program will identify a SCID case. Dr. van Dyck stated that he did not think it was the role of the Committee to decide who should do something or to advocate activities done to get conditions added to the uniform newborn screening panel. The Advisory Committee reviewed the evidence for SCID and found gaps in information needed to make a recommendation; when those gaps are filled, the Committee will consider nomination again. Dr. Howell agreed.

Additional comments by Committee members on specific points in the list proposed by Dr. Vockley included the following:

- **List item #1.** Dr. Boyle said it is important to specify what the denominator should be for the identification of a confirmed case of SCID.
- **List item #2.** Dr. Chen asked what the rationale for requiring a false positive rate for SCID screening of < 0.1 percent was, noting that this would mean there was 100 false positives for one true positives. Dr. Calonge said < 0.1 percent false positive rate does cause some harm, but weighing it against benefits of early detection of SCID leads to the conclusion that screening confers a net benefit. Dr. Rinaldo observed that for tandem mass spectrometry (MS/MS), the false positive rate for disorders already on the newborn screening panel can easily be above 1 percent and can even be close to 3 percent, so a false positive rate of 0.1 percent is actually a very high standard.
- **List item #3.** Dr. Boyle and Dr. Watson noted that many state screening laboratories lack the ability to screen for SCID using a molecular test. Dr. Getchell recommended changing the wording to "demonstrated willingness and ability of another state screening lab." Dr. Rinaldo also suggested adding language about a commitment of a state lab to a start date. Dr. van Dyck expressed concern that the two state labs screening for SCID now are using different tests. Dr. Rinaldo recommended that the Committee not require a single test but allow natural selection to sort out which test works best and is the most cost-effective. Also last one, need to say something about costs. Dr. Getchell said that before she wanted to implement a screening test in Delaware, she would want the test issue to have been sorted out. Dr. Alan Hinman, speaking from the audience, said that the discussions of the previous day had suggested that the information gaps with regard to the screening test for SCID were not so much the willingness of

another state to perform screening for SCID, but (1) reproducibility, especially with two different tests; and (2) the capacity of state labs to be able to perform the test. Dr. Mei Baker, speaking from the audience, said that the approaches Massachusetts and Wisconsin use are essentially based on the same principle.

- **List item #5.** Dr. Vockley noted that this item is not is really not a gap in information, just an alert to people in Washington, D.C., that they should provide resources to help achieve the other items. Dr. Getchell recommended adding some idea of the cost in this item.

Dr. Lloyd-Puryear raised a concern that the recommendations presented by Dr. Vockley were too vague to be translated into a letter to the HHS Secretary. Dr. Howell suggested that the Committee might want to adopt a policy of not sending letter to the HHS Secretary unless it had voted to recommend "including" or "not including" a condition on the uniform newborn screening panel. For SCID or conditions for which more evidence was needed, the Committee would send its decision and letter about the gaps in evidence to the nominator of the condition but not to the Secretary. Other Committee members agreed that the Committee should not send a letter to the HHS Secretary until it had evidence that sufficient to recommend either that a condition be included or not included on the core newborn screening panel.

Dr. Fleischman said he believed the minutes of the meeting should reflect that the Evidence Review Workgroup's excellent review of the evidence SCID did not allow the Committee to come to a conclusion that SCID ought to be recommended for screening, but that the Committee recognized the critical nature of the disorder and the likelihood that the evidence would be sufficient with small additional amounts of information or data. For that reason, the Committee voted to "recommend not adding SCID to the uniform panel now, and identifies specific gaps in the evidence for SCID that remain to be filled," with the idea that appropriate agencies would make resources be available to facilitate this action, so that in a short period of time, the evidence-based review would be sufficient Dr. Howell concurred that this is what the minutes should reflect.

Dr. Howell said that his recollection was that in the letter sent back to the Pompe disease nominator that the Committee did not include a chart indicating what information was still needed and stated that he thought it was important to include a chart for SCID.

D. Approval of Revisions to Operating Procedures for the Advisory Committee—Dr. Lloyd-Puryear

Dr. Lloyd-Puryear reported that she had changed the Committee's operating procedures because the General Services Administration told her that some things from the Committee's newly approved charter needed to be included in the operating procedures. The Advisory Committee voted unanimously to approve the Advisory Committee's newly revised operating procedures:

- **MOTION #6 (APPROVED): The Advisory Committee approves the newly revised document "ACHDNC: Policies and Procedures for the Operation and the Development of Recommendations for Screening Newborns and Children for Heritable Disorders and for the Heritable Disorders Program."**

E. Plans for Upcoming 2009 Advisory Committee Meetings

Dr. Howell noted that the dates for the Advisory Committee's next meetings are as follows:

- **May 12, 2009 (virtual meeting from 1:00–5:00 p.m.)**
- **September 24-25, 2009 (face-to-face meeting)**

Dr. Howell said that there would be a preliminary review of Krabbe disease at the May 2009 virtual meeting. Dr. Lloyd Puryear noted that Krabbe disease is the last condition for review in the pipeline, so if the Committee wants the Evidence Review Workgroup to do any other items, it should indicate that quickly. Dr. Rinaldo said the fact that no conditions have been nominated after Krabbe may just mean that nothing is ready. Potential nominators need to learn from the first two conditions that there is a need to have prospective, population-based screening for a condition, as well as identified cases of the condition through population-based screening.

Dr. Howell asked Committee members to give Dr. Lloyd-Puryear their suggestions for additional agenda items for upcoming meetings:

- Dr. Dougherty suggested that the Committee consider what to include in the report on "newborn screening guidelines" that the Advisory Committee is required by the Newborn Screening Saves Lives Act and new charter to produce in 2 years. Dr. Howell said that this discussion could begin at the May meeting.
- Dr. Kus and Dr. Boyle suggested that the Advisory Committee discuss what it's role with respect to repositories of dried blood spots should be. Noting that this type of discussion would benefit from a face-to-face meeting and would require public dialogue, Dr. Howell said this could be included on the agenda for the September meeting.

F. Other Committee Business

Dr. Howell suggested that the Committee might want to think about expanding its scope a bit. Noting that the Advisory Committee's new charter requires the appointment to the Committee of an expert in infectious diseases and a professional ethicist, he said that there is considerable interest in screening newborns for infectious disease (e.g., cytomegalovirus). There is also some in using hospital-based technologies such as oxygen saturation in identifying potential fatal heart disease in newborns. There also may be some things that certain states are screening for that the Committee ought to think about.

Dr. Howell drew Committee members' attention to a publication from the President's Council on Bioethics entitled *The Changing Moral Focus of Newborn Screening* that was distributed to them. Noting that the council had refused to have members of the Advisory Committee on Heritable Disorders in Newborns and Children appear before it, Dr. Howell said the Committee may want to discuss this publication at some point.

Dr. Howell reported that he had asked Dr. Vockley to chair the Committee's Internal Working Group that looks at conditions nominated and priorities. Dr. Rinaldo is officially leaving the Advisory Committee, but Dr. Howell said he hoped that he would continue to serve on the working group. Dr. Howell said he had also asked Dr. Harry Hannon and Dr. Calonge to serve on that working group. Dr. Rinaldo said it had been an honor and a privilege to work with the Committee.

Finally, with no other business at hand, Dr. Howell adjourned the meeting at 2:10 p.m.

***

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

/s/ _____

R. Rodney Howell, M.D.
ACHDNC, Chair

/s/_____

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

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

APPENDIX A: WRITTEN PUBLIC COMMENTS ON THE NOMINATION OF SEVERE COMBINED IMMUNODEFICIENCY SYNDROME (SCID)

1. Jennifer M. Puck, M.D., SCID Nominator, Department of Pediatrics, University of California–San Francisco
2. Mei W. Baker, M.D., Assistant Professor, Department of Pediatrics, Science Advisor, Newborn Screening Program, State Laboratory of Hygiene, University of Wisconsin–Madison
3. Barbara Ballard, Parent and Administrator, SCID Network of Families
4. Marcia Boyle, President and Founder, Immune Deficiency Foundation

1. Jennifer M. Puck, M.D.
SCID Nominator
Department of Pediatrics
University of California–San Francisco
Statement to the HHS Advisory Committee
on Heritable Disorders in Newborns and Children
February 26, 2009

I am very pleased to have the Committee considering severe combined immunodeficiency (SCID), which I believe I was the first nominator for, and I don't want to talk very long because I think there is some exciting new data coming from the Immune Deficiency Foundation and SCID Family Group.

However, I just want to remind people that we all know about David "the Bubble Boy, who made SCID famous by being born and placed into a germ-free environment, but we don't often think about David's older brother who was born with SCID and not recognized early and died. His brief life was the tragedy that made the recognition of David "the Bubble Boy" possible.

I think this is a theme that is recurrent. Most families have only a sporadic occurrence of SCID. So they are not expecting it, and people don't think of it because infections are very much the rule in young babies. So SCID is often not discovered until it is too late.

I think newborn screening is a terrific opportunity to save babies from the family of the Bubble Boy on, and that is really my only comment. I am enjoying listening to this discussion. Thank you.

2. Mei W. Baker, M.D.
Assistant Professor, Department of Pediatrics
Science Advisor, Newborn Screening Program
State Laboratory of Hygiene
University of Wisconsin–Madison
Statement to the HHS Advisory Committee
on Heritable Disorders in Newborns and Children
February 26, 2009

Severe combined immunodeficiency (SCID) is a group of immune defects that block normal T-cell development and is uniformly fatal early in life—unless patients undergo successful allogeneic stem-cell transplantation. SCID is ideally suited for newborn screening (NBS) for several reasons: (i) the prevalence is estimated to be 1 in 66,000, (ii) effective treatment is available, and early identification and intervention result in significantly improved survival, and (iii) confirmation tests are readily available.

A proposed newborn screening test for SCID involves quantitating the number of T-cell receptor excision circles (TRECs) using newborn screening specimens. TRECs result from the productive rearrangement of the T-cell receptor and are found in normal naïve T cells, which are consistently absent or low in all SCID patients.

With funding from the Jeffrey Modell Foundation, the Children's Hospital of Wisconsin Foundation, the Children's Research Foundation, and the Wisconsin State Laboratory of Hygiene, a scientist team in Wisconsin has optimized the use of RT-qPCR to quantitate TRECs for screening SCID in newborns, and began to implement the screening test on all newborns in Wisconsin in January 2008. We will continue our screening for our SCID pilot study with grant support from the Centers for Disease Control and Prevention (CDC) received in October 2008.

Our year 2008 experience, as summarized in the evidence review group report, indicates that screening all newborns for SCID is feasible with minimal screening false positives. Quantitating the number of TRECs on newborn dry blood spots identifies infants with primary immunodeficiency.

3. Barbara Ballard

Parent and Administrator
SCID Network of Families
Statement to the HHS Advisory Committee
on Heritable Disorders in Newborns and Children
February 26, 2009

I would like to thank the committee for this opportunity to represent the families of children with Severe Combined Immune Deficiency. My name is Barbara Ballard and I am the mother of a boy with X-linked SCID. I am also the administrator for group of SCID families dedicated to supporting one another in this journey we call SCID row.

It was 25 years ago this week that David Vetter, the "Texas Bubble Boy" died. Despite being diagnosed as a newborn, it took doctors years to offer any treatment other than a plastic bubble because transplants were only an option if you had a matched donor. There were no donor registries, PEG-ADA had not yet been developed, and half matched transplants would not be available for more than another decade. Today bone marrow transplants are the standard of care for the majority of SCID patients. An effective method to diagnose SCID from a simple blood spot now exists. SCID families passionate to improve the rate of diagnosis have given their children's very blood toward improving the rate of diagnosis.

Let me talk a moment about quality of life for those children who are lucky enough to be survivors of this disease. I specifically want to talk about those children who were not diagnosed as newborns, those children who had to be so sick that they came to the brink of death before doctors could diagnosis the problem. My son Ray is one such child. Ray is now 15 years old. Born seemingly normal, he thrived for several months until he caught his first cold. Within days of first entering my pediatrician's office with a child that I thought might have a virus, he was in the PICU and on a ventilator with PCP pneumonia. He spent 4 ½ months on a ventilator, had 13 chest tubes, and was trached. He received his first bone marrow transplant at a year old while on the ventilator in the Duke PICU. An enteral virus ultimately caused severe GI damage. His GI tract never fully recovered and he remains fed by enteral and parenteral means. Infection and graft vs. host disease caused his graft to fail and he has required two additional booster transplants. He managed to come off the ventilator and his trach was eventually removed, but he has severe lung damage and scarring which significantly limits his ability to participate in normal childhood activities. All the infections had to be countered with multiple antibiotics, antivirals and antifungals. Ultimately, we learned that one of the antibiotics used to save his life, had also left him deaf.

My son's medical costs maxed out a $2million insurance policy by the time he was 5 years old. Though Ray survived when many have not, his life will continue to have many costly challenges which could have been prevented. Benefits of early diagnosis for him would have been a life without these ongoing costs and challenges.

My son is not alone in having long-term medical complications resulting from a delay in diagnosis. As the administrator for a support group of SCID families, I can tell you many similar stories. It is for all the SCID children, surviving and lost, that I speak today.

Modern viruses are becoming more of a risk even to the general population. The best way to battle many of them has been the development of live virus vaccines. It is now considered "safe" to give a live rotavirus vaccine to an infant who is only 6 weeks old. How is a pediatrician to know that a 6-week-old infant has SCID, unless there is a mandatory screening test for newborns? The manufacturers' own literature tells you to "check with your doctor if your baby's immune system is weakened". The vials in which the vaccine is delivered must be disposed of in a biohazard waste container. It is unconscionable that the administration of a live vaccine to children as young as 6 weeks has been approved without first providing a method to identify those children for whom this vaccine could be devastating. The responsibility to protect those children who are most at risk of injury from these vaccines now lies with you, the members of this committee. As more live virus vaccines are developed to protect the general population it compounds the risk to our undiagnosed SCID babies and compounds your obligation to protect them.

There are those who would argue that a false positive test for SCID would be too dire for the family involved. I disagree. When I asked the SCID families their perspective on this argument; those families were overwhelmingly shocked to learn that there was more concern for a family with a healthy baby who might be asked to repeat a test, then for a family with an undiagnosed SCID baby who might not learn of that diagnosis until after they buried their child.

SCID is a disease which cannot be seen or identified at birth without a blood test. Children with SCID are born looking and acting seemingly normal. A simple and reliable test for SCID now exists. We can easily identify affected children before they contract their first cold. Without this early diagnosis and the now standard medical treatments, the damage caused by infections allowed to ravage the bodies of these children, will cause irreversible damage and very often death. How many children must suffer with a diminished quality of life, how many children must die before you say that it's too many? We have the technology, we have the science, we now need the prudence to step up to the plate and make this test a standard of care.

4. Marcia Boyle
President and Founder
Immune Deficiency Foundation
Statement to the HHS Advisory Committee
on Heritable Disorders in Newborns and Children
February 26, 2009

IMMUNE DEFICIENCY FOUNDATION

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I want to thank the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children for giving me the opportunity to comment in favor of adding Severe Combined Immune Deficiency (SCID) to newborn screening panels.

Founded in 1980, the Immune Deficiency Foundation (IDF) is the national patient organization dedicated to improving the diagnosis, treatment, and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research.

The federal government conducts the National Health Interview Survey, the National Health and Nutrition Examination Survey and funds the Behavioral Risk Factor Surveillance Surveys to better understand the incidence and prevalence of common acute and chronic conditions in the population. Less common medical conditions, like primary immunodeficiency diseases, are not tracked in these studies. Consequently, as part of its mission to improve the health of persons with these conditions IDF conducts surveys to better understand these diseases, their treatment, and the outcomes. Because of the unique problems of our SCID families, IDF initiated a special survey of these families to understand their experiences with diagnosis and treatment. We developed a national sample of 208 families identified as having a family member with SCID from the IDF database, the SCID forum database, and the SCID Angels for Life database. The survey was conducted as a self-administered interview by Web and mail between January 13 and January 30, 2009. Despite such a brief field period, with only one email and one email reminder, and one regular mailing, we achieved a 63.5% response rate, with 124 eligible families with a total of 156 SCID cases in those households as the basis for this analysis. (Figure 1). This data is preliminary, as more responses came in after the cut off period for this analysis.

Findings:

In households with any SCID cases, 80% of families reported one diagnosed child, 15% reported 2 children, and 6% reported 3 children, for a total of 156 SCID cases. Of this group, 59 children, or 38% have died. This is a true tragedy, since we know SCID is curable if diagnosed and treated early. Indeed, 30% of these children were not diagnosed until after they died. If we had newborn screening, these children could be alive today. (Figure 2)

The data that follows is based on the respondents answering about their oldest surviving child with SCID, or if none have survived, the oldest deceased child. Out of these 124 cases, 20 were tested at birth due to a family history of SCID, and therefore were spared becoming infected prior to diagnosis. A total of 104 parents of SCID patients not tested at birth were asked about the time of symptom onset vs. time of diagnosis for those children. The survey demonstrates again the early onset of SCID symptoms with a mean age of 11.3 weeks and a median age of 8 weeks at symptom onset. Age at diagnosis, sadly, is much later than symptom onset for those not diagnosed at birth with a mean age at diagnosis of 26.1 weeks and a median age of 24 weeks. The age of diagnosis is three times the age at symptom onset. As medical literature points out, with SCID children, it's important to avoid the opportunistic infections that can severely disable or kill them. The current average delay in diagnosis after symptom onset is the difference between life and death. Newborn screening and the early initiation of treatment could prevent most SCID children having such infections. (Figure 3)

Not surprisingly, 90% of children had to go to a major medical center for diagnosis, with only 5% at a physician's office. 80% of cases were diagnosed in the same city or state where they live. (Figures 4, 5)

Nearly nine out of ten SCID children (89%) received definitive treatment for the condition. Of the treatments reported, 95% were bone marrow transplant, 2% were gene therapy, and 11% were Peg-ADA. Nearly half (45%) of patients were treated in the same city or state in which they live. (Figure 6)

Only thirteen children (11%) never received treatment for the condition. Of these, 85% had died (62%) or had become too ill (23%) to receive treatment. No one reported that a child was not treated because treatment was not affordable or available. It is late diagnosis, not the cost or availability of treatment, which is the barrier to care for these children. (Figure 7)

According to the article published in the New England Journal of Medicine, Feb. 18, 1999, "Hematopoietic Stem-Cell Transplantation for the Treatment of Severe Combined Immunodeficiency," authored by Dr. Rebecca Buckley, et al, if a bone marrow or stem cell transplant occurred before 3.5 months of age, 95% of SCID infants in their series at Duke University survived, as compared to only 76% who were treated when they were 3.5 months or older. Updated data from the Duke University

Medical Center shows a 96% survival rate for 48 SCID infants treated in the fist 3.5 months of live, and a 66% survival rate for infants treated after 3.5 months. (Figure 8)

In our survey, only 23.7% of patients were treated by 3.5 months, 50% were treated by 6.5 months, and 75% were treated by 9.2 months. Consequently, the vast majority of SCID cases in our survey received treatment significantly later than the period of 3.5 months quoted by Dr. Buckley Those in our survey who were diagnosed early and treated by 3.5 months had a 91% survival rate. Those treated after 3.5 months, had a 76% survival rate. Thus the findings from our survey of 109 treated SCID cases mirror those of Dr. Buckley's study. (Figure 9)

Of our respondents who had a SCID child who received treatment, 79% reported that the child was still living, and 21% reported the child is deceased. 82% of those still alive (mean age of 8.6 years) report that they currently see a specialist for SCID. Over half of these children don't need to visit a transplant specialist more than every 6 to 12 months, with 11% reporting every 2 years. (Figures 10, 11).

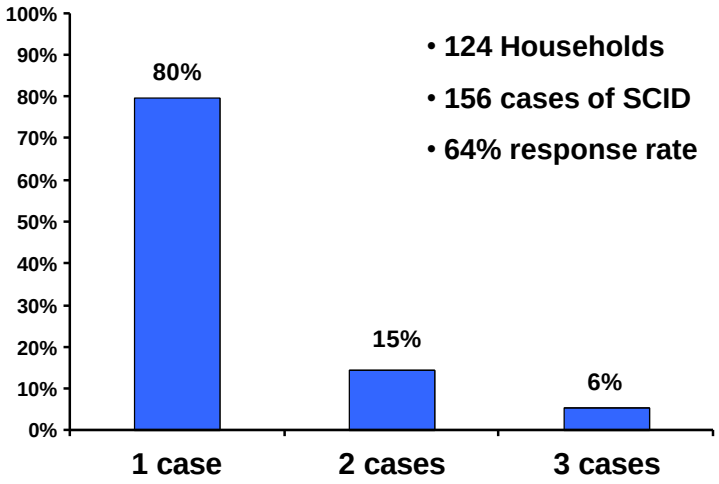
Very importantly, the average age at treatment in weeks was 29 weeks for those who are alive, and 58 weeks for those who are deceased. As you can see, this is significant at the 95% confidence level. (Figure 12)

Conclusions:

Without treatment, Severe Combined Immune Deficiency Diseases are fatal, because those with the condition have no protection from the infectious agents that surround us. These viruses and bacteria, for which the rest of us have natural immunities, produce uncontrolled infections in SCID children. This survey demonstrates that timely diagnosis and treatment makes the difference between life and death for these children. Moreover, the survey demonstrates that very early diagnosis and treatment is the real key to survival, but without newborn screening this is not available for the great majority who lack a family history. If disease is recognized only as a result of infection, it is often too late for effective treatment. Hence, screening at birth can mean the difference in a life measured in many years, rather than in weeks. Given this data, it would be inconceivable to me that the committee would not vote in favor of adding SCID to the Newborn Screening panel. Thank you again for your interest and time. And thank you for a vote to save lives and unnecessary suffering.

Figure 1

Number of Diagnosed SCID Cases in Each Household

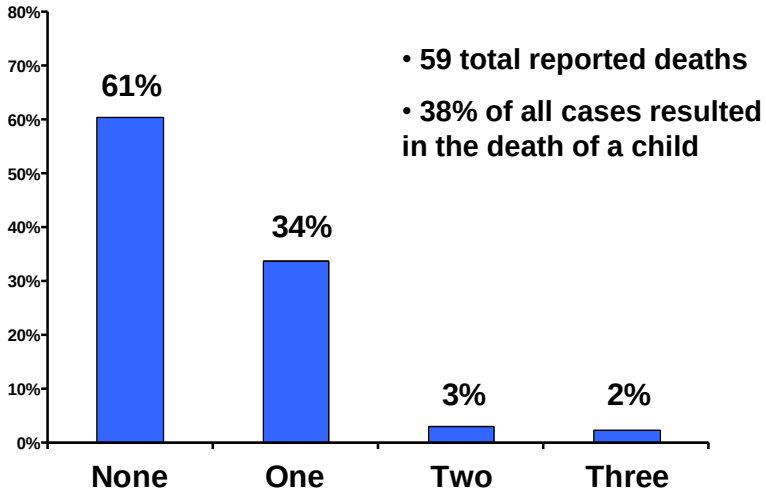


Q2a. How many people have ever been diagnosed with SCID in your household? (N=156)

Source: 2009 IDF SCID Survey

Figure 2

SCID Deaths in Households



Q2b. How many if any have died? (N=156)

Source: 2009 IDF SCID Survey

Figure 3

SCID Symptom Onset & Age of Person in Weeks at Diagnosis

Age of Symptom Onset	Age at Diagnosis
Mean: 11.3 Median: 8.0	Mean: 26.2 Median: 24.0

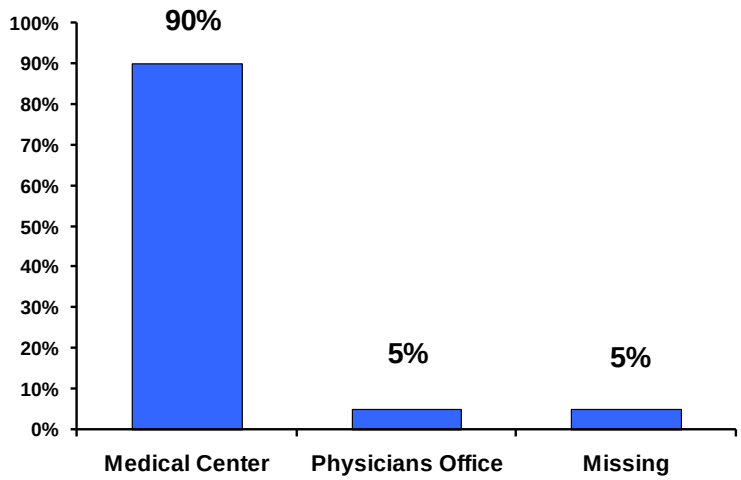
25% diagnosed by 3.2 months
50% diagnosed by 5.5 months
75% diagnosed by 7.4 months

Q2e_1. At what age (in weeks) did the person first start having symptoms of SCID? Base: Those not tested at birth due to family medical history (N=104)

Source: 2009 IDF SCID Survey

Figure 4

Location of Patient Diagnosis

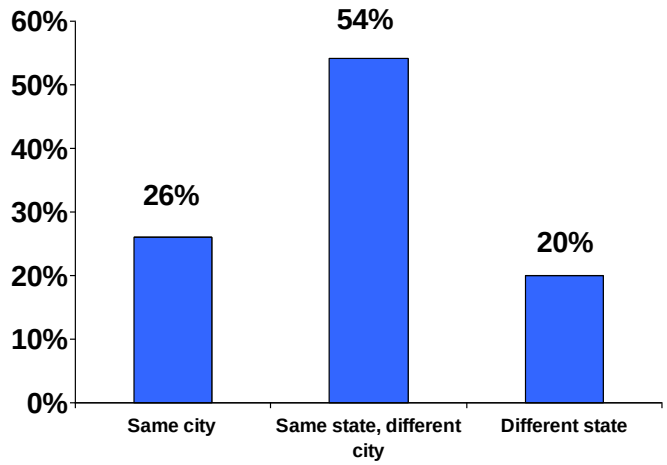


Q7a. Was the patient diagnosed at a medical center or at a physicians office? (N=124) Base: oldest surviving child with SCID/ oldest deceased if no surviving SCID

Source: 2009 IDF SCID Survey

Figure 5

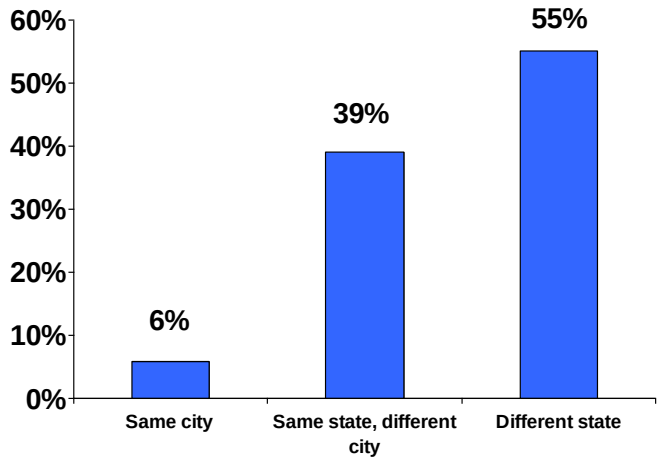
Travel for Diagnosis



Source: 2009 IDF SCID Survey

Figure 6

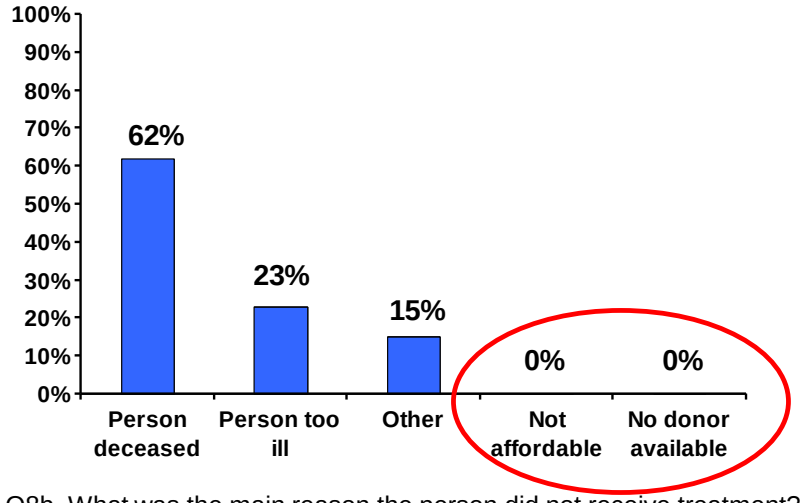
Travel for Treatment



Source: 2009 IDF SCID Survey

Figure 7

Reason Person Not Treated



Q8b. What was the main reason the person did not receive treatment?
(N=13) Base: Those diagnosed but not treated

Source: 2009 IDF SCID Survey

Figure 8

The NEW ENGLAND JOURNAL of MEDICINE

Volume 340:508-516 February 18, 1999 Number 7

Hematopoietic Stem-Cell Transplantation for the Treatment of Severe Combined Immunodeficiency

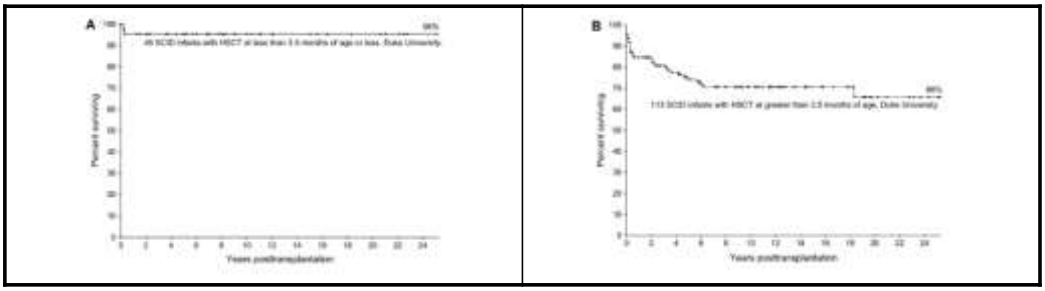
Rebecca H. Buckley, M.D., Sherrie E. Schiff, B.S., Richard I. Schiff, M.D., Ph.D., M. Louise Markert, M.D., Ph.D., Larry W. Williams, M.D., Joseph L. Roberts, M.D., Ph.D., Laurie A. Myers, M.D., and Frances E. Ward, Ph.D.

"Of the 22 infants who received transplants before they were 3.5 months old, 21 (95 percent) survived, as compared with 51 of 67 (76 percent) who received transplants when they were 3.5 months or older (P=0.088)."

<u>*Updated data from Duke University Medical Center:</u>

(A) - 48 SCID infants treated in first 3.5 months of life: 96% survive

(B) -113 SCID infants treated AFTER 3.5 months of life: 66% survive



* Kaplan-Meier PlotS reprinted from: J ALLERGY CLIN IMMUNOL 2007; 120 (4): 760-768, *Population-based newborn screening for severe combined immunodeficiency: Steps toward implementation* , Jennifer M. Puck, MD

Figure 9

Treatment in Months by Mortality: 2009 IDF SCID Survey

IDF 2008 National Survey of Severe Combined Immunodeficiency

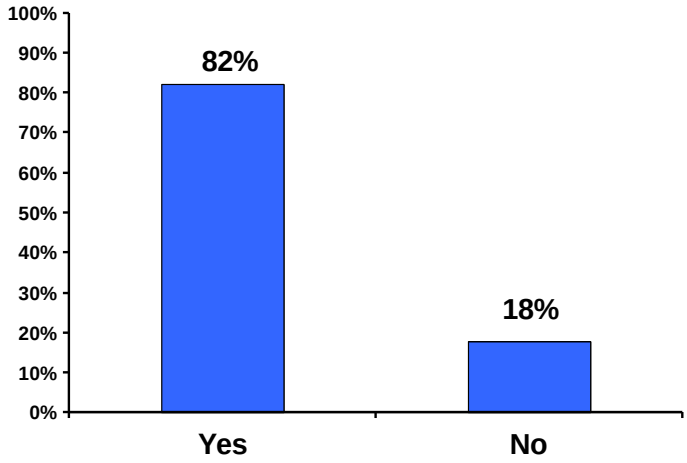
		Mortality		Total
		Deceased	Alive	
Treated by 3.5 months	Count	2	21	23
	%	8.7%	91.3%	
Treated after 3.5 months	Count	21	65	86
	%	24.4%	75.6%	
Total	Count	23	86	109
	%	21.1%	78.9%	

P = .08, Fisher's exact test

Source: 2009 IDF SCID Survey

Figure 10

Specialist Visits for SCID

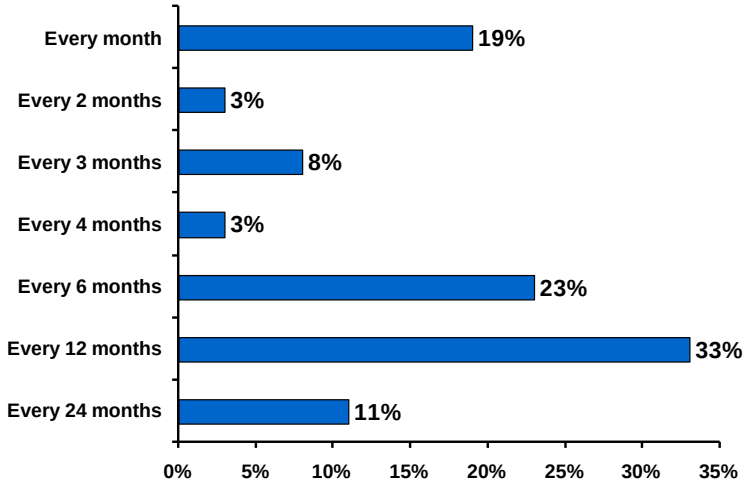


Q14. Does the patient currently see any type of specialist specifically for SCID?: Base: Those reporting treatment (N=86)

Source: 2009 IDF SCID Survey

Figure 11

Frequency of Transplant Specialist Visits

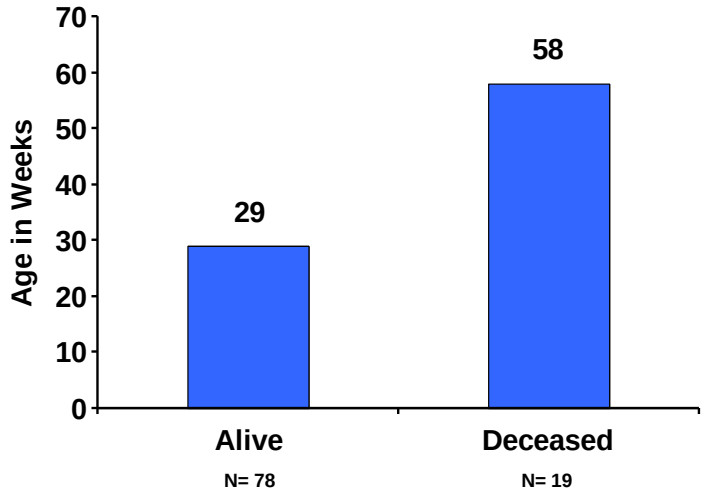


Q16. How often does the person visit the transplant specialist?: Base: Those reporting they see specialist (N=67)

Source: 2009 IDF SCID Survey

Figure 12

Average Age at Treatment in Weeks by Mortality*



Q11. What was the person's age at the time of treatment?, Q13a. Is this person deceased? **Base: All who reported treatment** (N= 97)

***P = .038**

Source: 2009 IDF SCID Survey,