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

Summary of 2nd Meeting
September 19-20, 2013
Webinar

FINAL

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (Committee) convened its 2nd meeting September 19 -20, 2013, as a webinar.

COMMITTEE MEMBERS

Don Bailey, Ph.D., M.Ed.
Distinguished Fellow
Early Childhood Development
RTI International
3040 East Cornwallis Road
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Phone: (919) 541-6488
Email: dbailey@rti.org

Joseph A. Bocchini, Jr., M.D.
(Committee Chairperson)
Professor and Chairman
Department of Pediatrics
Louisiana State University
Health Sciences Center in Shreveport
1501 Kings Highway
Shreveport, LA 71103
Phone: (318) 675-6073
Email: jbocch@lsuhsc.edu

Jeffrey Botkin, M.D., M.P.H.
Professor of Pediatrics and Medical Ethics
Associate Vice President for Research
University of Utah
Research Administration Building
75 South 2000 East #108
Salt Lake City, UT 84112-8930
Phone: (801) 581-7170 or 7171
Email: jeffrey.botkin@hsc.utah.edu

Charles Homer, M.D., M.P.H.
Chief Executive Officer and President
National Initiative for Children's
Healthcare Quality
30 Winter Street, 6th Floor
Boston, MA 02108-4720
Phone: (617) 391-2702
Email: chomer@nichq.org

Fred Lorey, Ph.D.
Genetic Disease Screening Program
California Department of Public Health
850 Marina Bay Parkway
Richmond, CA 94804
Phone: (510) 412-1490
Email: fred.lorey@cdph.ca.gov

Stephen McDonough, M.D.
Medicenter One Health Systems, Inc.
Department of Pediatrics
222 7th Street, N
P.O. Box 5505
Bismarck, ND 58502-5505
Phone: (701) 323-5355
Email: smcdonough@mohs.org

Dietrich Matern, M.D.
Department of Laboratory Medicine
and Pathology
Mayo Clinic
200 First Street S.W.
Rochester, MN 55905
Phone: (507) 538-1581
Email: dietrich.matern@mayo.edu

Alexis Thompson, M.D.
Division of Hematology/Oncology
Children's Memorial Hospital
2300 Children's Plaza Box #30
Chicago, IL 60614
Phone: (773) 880-4562
Email: athompson@luriechildrens.org

Catherine A. L. Wicklund, M.S., C.G.C.
Northwestern University
Feinberg School of Medicine
Center for Genetic Medicine
676 N. St. Clair, Suite 1280
Chicago, IL 60611
Phone: (312) 926-7468
Email: c-wicklund@northwestern.edu

Andrea M. Williams, B.A.
The Children's Sickle Cell Foundation, Inc.
617 Gearing Avenue
Pittsburgh, PA 15210
Phone: (412) 853-9883
Email: awilliams@cscfkids.org

EX-OFFICIO MEMBERS

Agency for Healthcare Research and Quality
Denise Dougherty, Ph.D.
Senior Advisor
Child Health and Quality Improvement
540 Gaither Road
Rockville, MD 20850
Phone: (301) 427-1868
Email: denise.dougherty@ahrq.hhs.gov

Centers for Disease Control and Prevention
Coleen A. Boyle, Ph.D., M.S.
Director
National Center on Birth Defects and
Developmental Disabilities
1825 Century Center Boulevard
Mailstop E86
Atlanta, GA 30345
Phone: (770) 488-7571
Email: cab3@cdc.gov

Food and Drug Administration
Kellie B. Kelm, Ph.D.
Scientific Reviewer/Biologist
Division of Chemistry and
Toxicology Devices
Office of In Vitro Diagnostic Devices
Evaluation and Safety
10903 New Hampshire Avenue
WO66, Room 5625
Silver Spring, MD 20993-0002
Phone: (301) 796-6145
Email: kellie.kelm@fda.hhs.gov

Health Resources and Services Administration
Michael Lu, M.D., M.P.H.
Associate Administrator
Maternal and Child Health Bureau
5600 Fishers Lane, Room 18-05
Rockville, MD 20857
Phone: (301) 443-2170
Email: mlu@hrsa.gov

National Institutes of Health
Alan E. Guttmacher, M.D.
Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
31 Center Drive
Building 31, Room 2A03
Bethesda, MD 20892-2425
Phone: (301) 496-3454
Email: guttmach@mail.nih.gov

DESIGNATED FEDERAL OFFICIAL
Debi Sarkar, M.P.H.
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau
5600 Fishers Lane, Room 18A-19
Rockville, MD 20857
Phone: (301) 443-1080
Email: dsarkar@hrsa.gov

LIAISONS AND ORGANIZATIONAL REPRESENTATIVES

American Academy of Family Physicians
Frederick M. Chen, M.D., M.P.H., F.A.A.F.P.
Family Practitioner
Department of Family Medicine
University of Washington
4311 11th Avenue, NE, Suite 210
Seattle, WA 98195-4982
Phone: (206) 543-7813
Email: fchen@u.washington.edu

American Academy of Pediatrics
Beth Tarini, M.D., M.S., F.A.A.P.
University of Michigan Health System
300 North Ingalls Street 6C11
Ann Arbor, MI 48109
Phone: (734) 223-4416
Email: btarini@umich.edu

American College of Medical Genetics
Michael S. Watson, Ph.D., F.A.C.M.G.
Executive Director
9650 Rockville Pike
Bethesda, MD 20814-3998
Phone:(301) 634-7127
Email:mwatson@acmg.net

American College of Obstetricians and Gynecologists
Nancy C. Rose, M.D.
Chair, ACOG Committee on Genetics
Director, Reproductive Genetics
Intermountain Healthcare
5121 S Cottonwood Street
Salt Lake City, UT 84157
Phone: (801) 507-7431
Email: nancy.rose@hsc.utah.edu

Association of Maternal and Child Health Programs
Lisa Bujno, M.S.N., A.P.R.N.
Chief, Bureau of Public Health Systems, Policy, and Performance
New Hampshire Division of Public Health Services
29 Hazen Drive
Concord, NH 03301
Phone: (603) 271-4110
Email: lbujno@dhhs.state.nh.us

Association of Public Health Laboratories
Susan M. Tanksley, Ph.D.
Manager, Laboratory Operations Unit
Texas Department of State Health Services
P.O. Box 149347
Austin, TX 78714
Phone: (512) 776-3106
Email: susan.tanksley@dshs.state.tx.us

Association of State and Territorial Health Officials
Christopher Kus, M.D., M.P.H.
Associate Medical Director
Division of Family Health
New York State Department of Health
Corning Tower, Room 2162
Albany, NY 12237
Phone: (518) 473-9883
Email: cak03@health.state.ny.us

Department of Defense
LTC Adam B. Kanis
Department of Pediatrics, MCHK-PE
Tripler Army Medical Center
Honolulu, HI 96859-5000
Phone: (808) 433-1876
Email: adam.kanis@us.army.mil

Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development
Genetic Alliance
4301 Connecticut Avenue, NW, Suite 404
Washington, D.C. 20008-2304
Phone: (202) 966-5557 ext. 211
Email: nbonhomme@geneticalliance.org

March of Dimes
Edward R.B. McCabe, M.D., Ph.D.
Senior Vice President and Medical Director
March of Dimes
1275 Mamaroneck Avenue
White Plains, NY 10605
Phone: (914) 997-4649
Email: emccabe@marchofdimes.com

National Society of Genetic Counselors

Cate Walsh Vockley, M.S., C.G.C.
Senior Genetic Counselor
Division of Medical Genetics
Children's Hospital of Pittsburgh
4401 Penn Avenue
Pittsburgh, PA 15224
Phone: (412) 692-7349
Email:catherine.walshvockley@chp.edu

Society for Inherited Metabolic Disorders

Carol Greene, M.D.
University of Maryland Medical System
Pediatric Genetics
737 West Lombard, Room 199
Baltimore, MD 21201-1596
Phone: (410) 328-3335
Email: cgreene@peds.umaryland.edu

Table of Contents

I. Administrative Business: May 16, 2013

A. Welcome and Roll Call

Joseph A. Bocchini, Jr. M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University
Shreveport, LA

Dr. Joseph Bocchini welcomed the webinar participants to the second meeting of the Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (Committee). Ms. Debi Sarkar, the Designated Federal Official (DFO), also greeted the committee members and organizational representatives and noted that more than 200 individuals had registered for the webinar.

Voting members present were:
Dr. Don Bailey, Dr. Bocchini, Dr. Jeffrey Botkin, Dr. Coleen Boyle, Dr. Denise Dougherty, Dr. Charles Homer, Dr. Kellie Kelm, Dr. Fred Lorey, Dr. Michael Lu, Dr. Stephen McDonough, Dr. Dietrich Matern, Dr. Alexis Thompson, Ms. Catherine Wicklund, and Ms. Andrea Williams.

Nonvoting organizational representatives present were:

- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- American College of Obstetricians and Gynecologists (ACOG): Dr. Mindy Saraco (Alternate for Dr. Nancy Rose, morning only)
- Association of Maternal and Child Health (AMCHP): Ms. Carolyn Mullen (alternate for Ms. Lisa Bujno)
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State and Territorial Health Officials (ASTHO): Dr. Christopher Kus
- Department of Defense (DoD): Dr. Adam Kanis
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes: Dr. Edward McCabe
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carole Greene

B. Committee Correspondence

Joseph A. Bocchini, Jr. M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University
Shreveport, LA

1. The Secretary's response to the Committee's letter regarding linking birth certificates to newborn screening. The Secretary decided not to accept the four recommendations, but noted that Department of Health and Human Service agencies expressed a willingness to assist states with newborn screening and data quality assurance.

C. **Approval of May 2013 Meeting Minutes**

Joseph A. Bocchini, Jr. M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University
Shreveport, LA

The Committee approved the minutes.

II. Assessing the Impact of the Committee's Recommendations on Long-Term Follow-Up on State Newborn Screening Programs

Beth Tarini, M.D., M.S., F.A.A.P
Organizational Representative
Professor, Child Health Evaluation and Research
University of Michigan Health System
Ann Arbor, MI

Dr. Tarini reported on the findings of a study funded by HRSA and the Genetic Alliance that examined the impact of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children's (SACHDNC) statement on long-term follow-up (LTFU) of NBS.

For the purposes of the study, LTFU was defined as beginning after the receipt of a diagnostic confirmation of a disorder as a result of an out-of-range NBS result. It includes "assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan of individuals identified with a condition included in newborn screening."[1] The SACHDNC, the immediate predecessor committee to the current Committee, developed its statement based on information shared during the Subcommittee on Follow-Up and Treatment's "Overarching Questions in Long-Term Follow-Up and Treatment in Newborn Screening" workshop. The SACHDNC published its guidance on this issue in the October 2011 issue of *Genetics in Medicine*. The study sought to determine the effect of the guidance on LFTU data collection by states. It is part of a larger project examining the policy impact of recommendations concerning conditions that are not on the Recommended Uniform Screening Panel (RUSP).

The study was targeted toward NBS follow-up directors and used a snowball sampling method to identify additional participants who could answer the questions in the web-based survey instrument. Data collection took place in three waves in July and August of this year. The survey addressed LTFU collection activities, barriers to LTFU, and general attitudes.

It was reported that 72 percent of the states responded to the survey. Twenty-four states provided complete responses to the survey; in some cases more than one respondent was required to obtain complete information. Respondents included NBS program managers, follow-up coordinators, NBS program directors, NBS program administrators, and genetics coordinators.

Findings of the study include:

- Twenty-one states actively collect LTFU data, seven states access existing data collected by public and private entities, six states contract out the collection of NBS data, and 12 states have no method for collecting data.

[1] Kemper, AR, et al. Long-term follow-up after diagnosis resulting from newborn screening statement of the U.S. Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Genet Med, 2008 Apr; 10(4):259-61.

- Concerning the use of SACHDNC article to guide the development of LTFU activities, 60.5 percent of indicated states used the article, and 39.5 indicated that they did not. The number of those that used the article to guide the development of LTFU activities correlates to those that actually collect LTFU data.
- The survey asked about the collection of eight types of data strongly representative of the data collected as part of a LTFU program (i.e., follow-up status, patient demographics, health care utilization, treatment regimen, patient access to services, cost, and enrollment in research studies). Highlighted findings included:
    - Follow-up status was the most commonly collected type of data (25 percent of respondents) and it was used primarily for purposes of monitoring or improving clinical care.
    - Twenty states collect data on treatment regimens, with the primary goal of improving monitoring and improving clinical care.
    - Tracking health outcomes was the most common reason 17 states collect health outcomes data.
    - Eleven states collect data on patient access to care for the purposes of monitoring and improving clinical care and connecting patients and families to support services and public health programs.
    - The chief reasons for collecting cost data cited by the six states collecting it were monitoring and improving clinical care and program evaluation.
- The survey asked about the methods used to collect and store data. Findings highlighted included:
    - The top methods for collecting data were by paper records (20 states) and by computerized methods (19 states). However, states most commonly used a combination of multiple collection methods.
    - The vast majority (68 percent) of states do not collect data directly from hospital or clinic electronic health records (EHRs).
    - Forty-seven percent collect data using a web-based portal system.
    - State registries were the most common type (47 percent) of computerized database from which LTFU programs collect data.
    - Most states (24) used computerized storage methods.
- Concerning barriers to LTFU, the survey used a Likert scale to identify barriers to collecting LTFU data and determine whether it is more difficult to collect data for some condition categories than for others. Highlights of the findings concerning barriers included:
    - States reported that it is most difficult to collect data for lysosomal storage disorders, Critical Congenital Heart Disease (CCHD), and immunologic disorders, all of which have only recently been added to the RUSP.
    - In states that do not collect LTFU data, work process barriers include regulatory requirements for data sharing; communications between physicians and NBS programs; consent issues; management of large, computerized databases; and variation in LTFU activities for each disorder. States that do collect data report less difficulty in collecting data, with the definition of the LTFU data elements that need to be collected as the primary barrier.
    - The primary structural barriers reported by states that do not collect LTFU data were the lack of a designated employee to oversee LTFU activities and the lack of statutory authority to oversee LTFU activities. Among states that do collect LTFU data, the lack of a designated employee was the most frequently cited barrier.
    - Organizational culture barriers were more widely spread among the survey options. Lack of clinician interest in LTFU activities was the chief barrier identified by states that do not collect data.
- With regard to general attitudes concerning LTFU, the study found that:
    - States that collect data tended to believe that LTFU activities are part of their responsibilities; those that do not collect data do not tend to believe it is part of their responsibilities. Some states that are collecting data have questions about whether they should be doing so and how much data they should be collecting.

- States that did not think conducting LTFU activities was their responsibility frequently identified specialists, the medical home, and programs for children with special needs as the entities responsible for LTFU.
- With regard to the feasibility of collecting LTFU data within five years, states that do not currently collect data indicated that it was not feasible to begin collecting in that time frame. States that do collect some data tended to believe that it would not be feasible to add categories.

In conclusion, two-thirds of the states collect LTFU data, with the types of data varying by state. Most states collect this data themselves and most do not use the SACHDNC statement to guide their collection efforts. Barriers to data collection are multifaceted and extend beyond resources and funding. She indicated that states may need guidance concerning LTFU, including assistance in prioritizing the types of data to be collected and identifying the goals of the collection efforts. These issues existed prior to the recommended addition of Pompe disease to the RUSP; however, LTFU data collection will become more important as disorders with late-onset phenotypes are added to the panel.

Committee Discussion

- It was indicated that the study did not consider the proportion of children served. It would be possible to include the number of children served as variable. This is not so important if the focus is quality improvement from a state perspective; it would be more important if the questions relate to improving clinical care and understanding metrics of care.
- A Committee member stressed the importance of understanding the impact of LTFU and the number of children for which information is available.
- A question was raised concerning whether states are collecting data on outcomes at the level of individual babies and whether state monitoring activity implies a responsibility to respond to the collected data. In response, it was indicated that the survey did not ask whether states were collecting individual or group level-data. She indicated that the question would apply to all public health registries.
- An organizational representative reported that Texas collects information at the individual baby level from physicians and data are used primarily for monitoring.
- A Committee member asked about barriers to LTFU, specifically with regard to funding sources and whether Title V programs are involved in LTFU. The presenter did not have information on the sources of funding. However, programs that rely on grant funding could risk their data collection effort if the funding dries up.
- With regard to where states obtain their data (e.g., clinicians versus families), it was stated that the study did not ask whether states collected parent-reported data in a systematic way.
- A Committee member pointed out the importance of understanding the extent of the information that is collected (e.g., the types of conditions collected, length of time after birth, etc.). It was acknowledged the usefulness of this type of data, but indicated that the study did not have the resources or the time necessary to collect this type of information from the states. There are disparities in LTFU with regard to conditions, with some states collecting for only a few conditions.
- In response to a question about states comparing their collection efforts to or learning from those of other states, it was indicated that this information could be found in the qualitative responses, which were not presented. Anecdotally, the survey sparked questions within some states concerning what they are a doing and what they should be doing.
- A Committee member noted the difference between block grants, which are regularly awarded, and other grants and noted that the mix of funding is what is important. He also noted that LTFU results in a system that collects data for the state and provides information for clinicians that provides benefits for both. The presenter agreed that the LTFU can be mutually beneficial. She also noted that states are trying to obtain the greatest return on their limited LTFU resources and might choose to focus on data or conditions that could be used to identify quality issues that could then be taken back to clinics and individual cases.

- In response to a question concerning what could be done with the LTFU data that is collected and whether it could be used to asses outcomes for variations in treatments, it was indicated that this study did not provide a sense of what is happening in this regard. She did not think that this type of work is taking place. The challenge is in developing collection methods that produce comparable data across conditions.
- An organizational representative reported that the Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) and the Newborn Screening Translational Research Network (NBSTRN) are discussing linking their LTFU datasets.
- Another organizational representative reported that the Follow-Up and Treatment Subcommittee is looking into the type of LTFU metrics needed and available data sources.
- In response to a question concerning state statutory requirements to maintain case registries and whether states are collecting data as part of their requirements, it was indicated that this was a side project within the study. Most statutes are vague enough that it is difficult to tell whether there is a responsibility to collect data. Few statutes include language that specifically directs data collection.
- It was also reported that the data in the presentation would be available in written form within 30 to 60 days. It will only be available for review within the Committee, as the completed report will be submitted for peer review.

III. Newborn Screening Clearinghouse – Baby's First Test CCHD Videos

Natasha Bonhomme, M.A.
Organizational Representative
Vice President of Strategic Development
Genetic Alliance
Washington, DC

In 2011, Children's National Medical Center (CNMC) received a Baby's First Test Challenge Award to create *Heart Smart* videos for parents and providers concerning CCHD.

The 6-minute parent video focuses on what parents might see if their child receives CCHD screening. It addresses the timing of the screening, how the screening is done, what the screening looks for, and next steps if an abnormal result is received. The video emphasizes that the goal is detection. Symptoms are described and parents are encouraged to contact their doctors if they have any concerns even if the screening produces a negative result.

The 12-minute provider video focuses more on training and includes more details on the screening. The video could be shown to decision makers within hospitals. The video discusses the changes in the heart structure, the complications associated with CCHD, the history of CCHD screening, the reasons CCHD was added to the RUSP, the screening procedure, and the way CCHD works in conjunction with other screening programs. The provider video also highlights the same family story featured in the parent video but provides more detail. Talking points for discussing the screening with parents are also included.

In 2012, multiple channels were used to disseminate the video including grand rounds at several hospitals. The Newborn Channel, which works with more than 1,000 hospitals in the United States, will include the English and Spanish versions of the parent video in their rotation beginning in October. CNMC and Genetic Alliance also received many international requests for the video and additional training concerning CCHD. Ms. Elizabeth Bradshaw and Dr. Martin traveled extensively, especially in the Middle East, to provide additional training. At the beginning of this year, CNMC and Genetic Alliance worked together to translate the parent video into Arabic, Chinese, French, Russian, and Spanish. All of the translated videos became available in July. They can found at http://www.babysfirsttest.org/newborn-screening/conditions/critical-

congenital-heart-disease-cchd, at http://www.childrensnational.org/Parenting/Specific-Conditions/cchd.aspx, on YouTube, and on DVDs that are disseminated free of charge. Users are encouraged to go to the YouTube video, download the video to DVD, and share it.

It was reported that there have been more than 7,000 views on all of the YouTube pages. Requests for the videos from the states continue to be received.

Committee Discussion:

- A question was asked concerning translation of the provider video. In response, it was indicated that there has been some discussion about it. It is anticipated that the decision would hinge on CNMC's willingness to do the translations. Awareness of the videos seemed to increase after the translation of the parent video, which has provided a better sense of the information that is needed and the topics in which people are interested.
- A Committee member asked if there are guidelines for use of the video (e.g., for pre-natal care, perinatal care, or a specific time period). Ms. Bonhomme hoped that the video would be used as early as possible, and indicated that they have received at least one request from an obstetrics and gynecology practice for the video.
- A Committee asked whether any of the national primary care organizations such as the AAP and AAFP have been asked to endorse the video and post it on their websites. Ms. Bonhomme replied that they have not been approached, but agreed that making the requests should be a next step for the project.
- With regard to a formal evaluation of the effects of the video, the presenter indicated that the Genetic Alliance would be interested in partnering with CNMC if the hospital has an interest in doing this work. She suggested that the partnership with the Newborn Channel opens up opportunities for assessment.

IV. Policy Impact of the SACHDNC Recommendations Regarding Sickle Cell Trait Screening in Athletes

A. Assessing the Impact of the NCAA SCT Screening on State NBS Programs

Beth Tarini, M.D., M.S., F.A.A.P
Organizational Representative
Professor, Child Health Evaluation and Research
University of Michigan Health System
Ann Arbor, MI

The National Collegiate Athletic Association's (NCAA) mandate concerning sickle cell trait (SCT) screening went into effect for Division I in August 2010. The mandate required Division I athletes to have a sickle cell solubility test, present documented prior test results, or sign a waiver as part of the pre-participation physical.

In October 2011, SACHDNC released recommendations that stressed that:

- All individuals should have the opportunity to learn their risk, including carrier status, for medical disorders including genetic conditions such as SCT;
- Evaluation and testing should take place within the medical home and include counseling and the assurance of privacy of genetic information;
- All potential athletes should receive education on safe practices for prevention of exercise and heat-related illnesses;
    - The Secretary of Health and Human Service should direct SACHDNC to work with public and private agencies and organizations to develop guidance and educational materials concerning SCT in all individuals, including athletes
- Genetic testing should not be pre-requisite for participation in sports unless deemed medically necessary: and

- The National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) conduct research to understand the increased risk of exercise-induced sudden death in those with SCT.[2]

Following the release of the SACHDNC's recommendations, the NCAA approved testing all Division II athletes in August 2011 and for Division III in January 2013. The Division III mandate included a requirement that athletes be educated about the implications of signing a waiver and that athletes waiting for test results or who have signed a waiver be given information concerning the risks and impact of SCT. Athletes were provided information on obtaining information on the results of NBS for sickle cell trait, which included obtaining information from the state in which they were born.

The purpose of the study was to assess the effect of the NCAA mandate on state NBS programs, specifically with regard to the demand on resources, programmatic changes, and variation in impact across programs. It is part of a larger effort to assess the policy impact of the Committee's recommendations concerning non-RUSP conditions. The overall study was funded by HRSA and the Genetic Alliance and is being presented to the Committee for comment only.

The study used telephone and written surveys and employed a snowball sampling method. Laboratory directors and personnel and follow-up directors and personnel were sampled. Each state's results were validated with all respondents. The domains assessed were:

- History and procedure of NBS for hemoglobinopathy, specifically laboratory procedure and history, availability of SCT results, and reporting of SCT status.
- Direct effects of the NCAA mandate regarding the volume and nature of the requests, procedures for providing results, and qualitative assessment of programmatic changes.

92 percent of states participated was, with 71 percent of states providing complete information.

Findings of the study regarding the history and procedure of NBS for hemoglobinopathy included:

- The range of dates during which states screened for SCT ranged from 1975 to 2005 (mean=1990), with most states using a two-step reflexive testing method.
- Availability of results varied by state. Availability was affected by the continuity, or lack thereof, of data storage systems (21 states), the inaccessibility of data systems (nine states), the disposal of records based on legal and regulatory requirements (seven states), and the lack of universal screening prior to 1995 (seven states). Only three states had continuous and easily accessible NBS screening records.
- Thirty-one states currently provide results.
    - Of these 59 percent provided the full NBS result, 11 percent provided only the SCT result, and 30 percent provide no results.
    - The vast majority of states (95 percent) allow primary care physicians to request results. A smaller percentage (34 percent) allows students to request the results. Some states also allow team physicians (45 percent), athletic departments (25 percent), and the NCAA (5 percent) to request results.
    - States have mostly provided results to primary care physicians (49 percent), team physicians (25 percent), and students (19 percent). Fewer than 10 percent of states have provided results to athletic departments and none have provided it directly to the NCAA.
- Reasons cited for not providing results included privacy of genetic information, NBS program policies, cost, accuracy of matching records to individuals, accuracy of the diagnosis (e.g., primary versus secondary finding or target), lack of records for particular age groups, difficulty of retrieving results, and resource allocation.
- NBS also cited concerns about providing results in terms of the NBS program mission and in terms of maintaining the public trust.

Concerning the actual effects of the NCAA mandate, it was reported that:

[2] This recommendation was not accepted by Secretary Kathleen Sebelius.

- The number of annual requests varied greatly from zero to 6,000 requests (including batch requests but not those made directly by individuals using a web portal), with most being received between May and August. Most programs received between one and 100 requests.
- Most surveyed states (64 percent) reported no burden associated with the requests. Of those reporting burdens, more programs reported time needed to respond (21 percent) as the burden than reported time and cost (15 percent). Anecdotally, Dr. Tarini reported that other state burdens included the demand on office equipment in a state that receives requests by fax, the need to prioritize responses to newborns over these requests, and the need to provide education on why the results are required. States without much capacity to provide results might actually have a lower demand due to their inability to provide results.
- Programmatic changes (qualitative) reported as a result of the mandate include creation of new forms, changes in policies on release of information, review of state requirements concerning the destruction of results, review educational materials, and changes in staffing.
- The mandate also results in NBS programs beginning to discuss issues such as the need for better information technology systems, such as online portals, and the length of time NBS results are retained for disorders other than SCT.

Conclusions formed from the study results were that some states are not capable of providing SCT results to student athletes, practices for sharing SCT results vary by state, and the impact of the mandate on states that report results vary widely.

Committee Discussion:
In response to a question concerning the quality of the testing, it was indicated that the survey did not ask about the type of testing that was being reported. States assessed the quality of their results based on the type of test and the validity and reported this to the researchers.

- With regard to concerns over security of the test results and attempts to obtain other people's results, the study did not ask about the processes used to verify the identity of the requesting individual. It was clear that the relevant statutes were not designed for this situation.

B. Update and Unintended Consequences

Alexis Thompson, M.D., M.P.H
Committee Member
Division of Hematology/Oncology
Children's Memorial Hospital
Chicago, IL

Update and Unintended Consequences
Dr. Thompson described the policy issues that have arisen among other stakeholders and some of the unintended consequences of the NCAA mandate.

The benefits of NBS for SCT are well-known. Newborns known to have SCT are more likely to survive than those whose condition is identified later. Data from large studies indicates that 98 percent of children with SCT will survive to adulthood. Universal screening began in New York in 1975, and New Hampshire was the last state to adopt it in 2006. By 1990, about 40 percent of states conducting SCT NBS; by 1995 it had risen to 76 percent. By 1995, most of the states with large populations that would be susceptible to SCT were screening; Georgia was the only state of this type that was not.

Many professional organizations have released statements on this issue, including:

- Sickle Cell Disease Association of America,

- American Society of Hematology (statement was endorsed by the American Society of Hematology/Oncology, American Public Health Association, APHL, Sickle Cell Disease Association of America, and American Society for Clinical Pathology),
- American College of Sports Medicine, and
- AAP/ACMG.

The American Society of Hematology (ASH) does not support testing or disclosure of SCT status as a prerequisite for participation in athletic activities. Instead, it recommends universal interventions to reduce exertion-related injuries and deaths, which is similar to the position of the U.S. armed services. It maintains that the NCAA policy has the potential to harm both the student athlete and the greater population with SCT. ASH also supports expanded bio-medical and population-based research on SCT as it relates to exertion-related illness and other conditions.

AAP does not have a specific position on SCT. In conjunction with ACMG, it published a statement that opposes carrier trait testing in minors when there are no health benefits associated with testing. Additionally, the statement advises against school-based testing or screening as the school environment is not conducive to voluntary participation, thoughtful consent, privacy, confidentiality, or counseling concerning results.

With regard to fulfilling the NCAA mandate, Dr. Thompson pointed out that the use of the solubility test is problematic. Other problems with the mandate include costs associated with having primary care physicians retest student athletes (some provisions have been made for testing conducted through colleges and universities).

The solubility test mandated by the NCAA has no practical use for primary NBS and is not used by any of the states because it is negative for hemoglobin C and in newborns, infants, and other with high levels of hemoglobin F. Additionally, the test does not distinguish between SCT and any other form of sickle cell disease. In emergency situations, it might be helpful in raising suspicions of sickle cell disease. The test can help distinguish between certain types of sickle cell disease.

Unintended consequences of the NCAA policy include a dramatic increase in requests for results, highly variable state policies and practices, and policy implications of the release of this information to third parties. Other unintended consequences that are being seen by clinicians include the expansion of mandatory SCT testing to high school athletes. More disturbing is the belief of parents with a child with SCT that they (the parents) should not exercise because they could imperil their own health.

One unresolved issue concerning SCT screening is whether SCT status is reliably determined by the testing method employed. Dr. Thompson also identified the variation in state practices regarding notification of results in the newborn period and resources available for notification and follow-up. Methods of retrieval at a much later date, the need for education concerning the retrieved results, the effects of the results on reproductive choices, and the potential health consequences of carrier status are all issues that need to be addressed in greater depth. Finally, issues surrounding the ease of provider access to this information have not been resolved.

Recommendations for the Committee to consider were:

- Should the SACHDNC's recommendations still stand?
- Is this an appropriate use of NBS?
- Should the Committee provide additional guidance concerning the response to the requests for results?
- How does this experience affect the wider discussion of carrier status for other conditions?

Additionally, the issue was raised on whether sickle cell is an exemplar condition for carrier testing, given the limited empirical evidence of the value of conducting testing later. This includes understanding what people do with the information about carrier status and the differing obligations of reporting to parents and children. Issues concerning disclosure are ongoing, as are

discussions concerning biomedical ethics considerations. Also, the logistical demands on public health entities must be considered.

Proposal for the Committee:

- Consider establishing an ad hoc working group to address the outstanding issues,
- Determine the appropriateness of providing feedback to the Secretary,
- Develop guidance for states on managing requests, and
- Envision a framework for the dissemination of trait status across other inherited conditions.

Committee Discussion:

- Concerning systematic efforts to collect data on outcomes/impacts from a clinical perspective, the presenter was unaware of any such efforts. Much of the information is anecdotal. There has been limited cooperation from the NCAA with efforts to collect this information from student athletes.
- A Committee member discussed whether the concern about the mandate for athletes is muddying the water concerning NBS screening for trait status and the education that should accompany it.
- The presenter agreed that it is important to understand why people need to be informed about their trait status. Informing parents of babies with sickle cell disease is important to prevent death. The reasons for knowing SCT status are less clear, especially in the absence of scientific evidence concerning the benefits. Beyond reproductive risk, there is little information or evidence with which state agencies and providers can frame conversations with individuals.
- The Committee member noted that the Sickle Cell Disease Demonstration Program legislation includes a requirement for reporting on the activities of participating states including efforts to identify and educate individuals with SCT. Another Committee member indicated that there are some other risks, aside from reproductive risks, associated with SCT. The rational for conducting the screenings should be tied to the way that individuals are informed about their status.
- A Committee member explained that SCT carrier follow-up is conducted by genetic counselors. This provides an opportunity for carriers to discuss this information and how to share it. She noted that targeted screening would not be desirable.
- A Committee member pointed out that student athletes who receive this information from a coach or trainer might not be receiving information on reproductive information.
- In response to a question concerning other organizations that are supporting the NCAA mandate, it was indicated that the trainers' association supports the mandate. The American College of Sports Medicine took a more nuanced response that supports non-discrimination and full participation. Many of the team physicians seemed surprised that ASH and other groups have the opinions that that they do.
- A Committee member questioned whether athletes and parents are contacting states to confirm status or whether the information they receive is new to them. This gets to the utility of disclosing trait status through NBS programs. Perhaps it would be better to offer trait testing to those who are considering reproduction, instead of relying on NBS to provide reproductive counseling decades before an individual considers having a baby.
- The presenter responded to a question about whether the NCAA policy was part of its legal settlement by stating that the NCAA has indicated this was what the association was willing to do in response to the family's request but indicated that the settlement is not public. NCAA has created a large number of written and video educational materials for student athletes and promoting an increased awareness of SCT. There are some questions about the science behind the information provided within the hematology community. The NCAA has also established a sports science institute to support research studies.
- An organizational representative indicated that there is a 1987 report that an association between SCT and death in Army recruits. The army response to this was universal precaution, not screening. The presenter responded that a later report found that the branches of the military that embrace universal precautions saw a reduction across all individuals compared to those that have not. It raises the possibility of providing a benefit through simple interventions without the potential harm from stigmatization. She also

cautioned against linking an association with causality. There is a need for more research on the metabolic myopathies that are disproportionally seen in African-Americans and whether these individuals might also have SCT.

- A Committee member asked about the different ways that individuals receive information concerning their SCT status when it comes directly from the state versus when it comes from athletic departments. It was indicated that the response varies by state. States have reached out to the schools and asked to work with them to develop educational materials but have been rebuffed. It is very difficult to determine what is actually happening when the information is provided to the athlete by the institution.
- An organizational representative reported that the NBS Clearinghouse also receive requests for information on how to obtain NBS results. The Clearinghouse contacted states and found that they gave similar responses to those reported by Dr. Tarini. She also noted that in most cases, the SCT result was new information for those who contacted the Clearinghouse.
- A request was made for more information concerning the existence of dialogue between the NCAA and the various professional associations that have made statements about the policy as well as whether there has been any outreach to the family concerning additional opportunities to address their core concerns.
- A Committee member pointed out that notification of the trait status of children often serves to inform the parents that they are at risk to have a child with the trait. Paternity can become issue in screening. This raises issues for whole exome screening, especially when carrier status is an incidental finding.

V. Committee Business: September 20, 2013

Joseph A. Bocchini, Jr. M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University
Shreveport, LA

Voting members present were: Dr. Bailey, Dr. Bocchini, Dr. Botkin, Dr. Coleen Boyle, Dr. Dougherty, Dr. Homer, Dr. Kelm, Dr. Lorey, Dr. Michael Lu, Dr. Christopher DeGraw (alternate for Dr. Lu in the morning session), Dr. McDonough, Dr. Matern, Ms. Melissa Parisi (alternate for Dr. Guttmacher), Ms. Wicklund, and Ms. Williams. Ms. Sarkar served as the DFO.

Nonvoting organizational representatives present were:

- AAP: Dr. Tarini
- ACMG: Dr. Watson
- ACOG: Ms. Saraco
- AMCHP: Ms. Carolyn Mullen (alternate for Ms. Bujno)
- APHL: Dr. Tanksley
- ASTHO: Dr. Kus
- DoD: Dr. Kanis
- Genetic Alliance: Ms. Bonhomme
- NSGC: Ms. Vockley
- SIMD: Dr. Greene

VI. Subcommittee Reports

A. Subcommittee on Laboratory Standards and Procedures

The Chair of the Laboratory Standards and Procedures Subcommittee reviewed their three main priorities:

- Priority A: Review new enabling/disruptive technologies.
- Priority B: Provide guidance for state NBS programs about decision making concerning implementation, integration, follow up, and quality assurance.
- Priority C: Establish processes for regular review and revision of the RUSP.

SUAC Implementation Study

The Subcommittee focused most of its efforts on a discussion concerning the Succinylacetone (SUAC) Implementation Survey. Subcommittee members were updated on the survey results and future steps.

Tyrosine is not a specific marker for Tyrosemia type I (TYR I). It is also elevated in other forms of Tyrosemia and other conditions. SUAC is a specific marker for TYR I, but it is not detectable by routine NBS.

Currently, fifteen (15) states still use tyrosine as the primary marker for TYR I. The majority of the states use SUAC. Two states use tyrosine as a primary marker and SUAC as a secondary marker. The survey looked at the differences between the states using tyrosine and SUAC and the barriers to moving to SUAC among the states still using tyrosine.

The survey researchers received 31 responses (16 SUAC states and 15 tyrosine states). Survey questions were tailored based on whether states used SUAC in dried blood spots as part of their NBS programs. The Subcommittee spent considerable time discussing the CDC's quality assurance, quality control, and proficiency testing program that includes TYR I, including the survey conclusions included:

- TYR I should remain on the RUSP.
- All U.S. NBS programs screen for TYR I.
- Several laboratories reported strong pushback for SUAC testing using a specific kit/method.
- Potential barriers to adoption of SUAC screening included funding, infrastructure, staffing, and technical expertise. No single barrier predominated.
- Eight of the 15 states that do not use SUAC screening indicated that recommendations from either the Committee or the HHS Secretary would not influence their decisions to adopt SUAC screening. Four indicated that such recommendations would.

The Chair of the Lab Subcommittee indicated that there are plans to publish the study. Additional actions concerning the results of the survey, such as whether the Committee should make a recommendation concerning SUAC, still need to be determined.

Updates

The Subcommittee members received an update on the Severe Combined Immunodeficiency (SCID) slide deck. The purpose of the slide deck is to provide NBS decision makers within states with information encouraging the addition of SCID to their NBS panels. The hope is that this slide deck would serve as a template for other conditions as they are added to the RUSP. Monthly calls for this project are ongoing.

APHL reported on APHL's celebration of the fiftieth anniversary of NBS, the NewSTEPS program, the mucopolysaccharidosis type I (MPS I) public health impact review, and the survey of states concerning the CDC's biochemical genetic testing recommendations. Some updates have already been made to the NewSTEPS website, and additional changes are scheduled for the near future. Updates include case definitions, quality indicators, and state profiles. The program is working with states to establish memoranda of understanding concerning data collection. APHL will begin work on the public health impact review for MPS I in preparation for presentation of

the condition to the Committee. Finally, APHL plans to conduct a survey of states assessing the implementation and use of the recommendation in the CDC's *Morbidity and Mortality Weekly Report* (MMWR) on biochemical genetic testing that has been presented several times in the past.

A new standing subcommittee of the Consensus Committee on Immunology and Ligand Assay is being formed. The Standing Subcommittee on Newborn Screening will parallel the pathway used for the Document Development Committees. The Subcommittee will review proposals and form working groups as needed to begin writing documents as needed.

The Subcommittee also discussed the changes in the Clinical and Laboratory Standards Institute (CLSI) nomenclatures that provide new, special designations for NBS documents. Issued NBS documents have all been reassigned new numbers, including the newest document concerning newborn blood spot screening for Pompe disease. The Chair of the Lab Subcommittee also reported that a work group will be established in the near future to address the harmonization of NBS terminology. The terminology would not be set in stone, and could be changed over time to address considerations and concerns as they arise.

Committee Discussion:

- The Chair of the Lab Subcommittee indicated that the Subcommittee spent some time brainstorming about new projects and that additional work needs to be done to narrow the questions to a project that the Subcommittee could undertake.
- A Committee member inquired about whether the CDC's consideration of including a report on TYR I in MMWR dovetails with the Subcommittee's work. Dr. Cuthbert indicated that CDC has determined what sort of publication it would like to develop on TYR I.

B. Subcommittee on Education and Training

The Chair of the Education and Training Subcommittee (E&T)briefly reviewed the Subcommittee's charge, which is to review educational and training resources, identify gaps, and make recommendations concerning a variety of groups including parents, the public, health professionals, screening program staff, and hospital/birthing facility staff. The Subcommittee committee meetings generate much interest from public or other advocacy groups as they address issues of interest to many of the parent groups.

Priority A: Promote NBS awareness among the public and professionals.
Current Subcommittee activities in support of this priority include providing input and support to the 2013 NBS Awareness Campaign. The Subcommittee received a report on activities associated with the celebration of the fiftieth anniversary of NBS. Dr. Bailey expressed the Subcommittee's appreciation to the CDC and APHL for their work on planning the many awareness activities supporting the year-long celebration.

The Subcommittee anticipates addressing the identification of goals and strategies for NBS awareness activities after 2013 in the near future. The Chair of the E&T requested that the Committee provide input on pressing awareness needs that should be addressed in the next several years.

Priority B: Provide better guidance for advocacy groups and others regarding the nomination and review process.
This priority developed as a result of questions about the review process from condition nominators. The Subcommittee sought to develop a document that would enable nominators to submit successful applications. The original project was to develop public-friendly summaries of previously conducted evidence reviews as well as of unsuccessful nominations (lessons learned). The nomination and review process has evolved, which might limit the usefulness of examples of earlier failed nominations. Over the summer, the Subcommittee revised the project with a goal of developing a public-friendly summary of the current nomination and review process that helps

nominators develop successful application packets. Lessons learned from earlier nominations that are still applicable to the current process might be included in the document.

Under the original scope of the project, HRSA contracted with Atlas Research to develop a draft document reviewing letters that were sent out in response to prior nominations. Because of the change in the focus of this project, the Subcommittee did not present a report on the Atlas document.

Under the revised activity, Atlas was asked to interview experts who closely associated with the Committee and familiar with the review process, review the existing framework and guidance documents, and prepare a snapshot summary based on the interviews and review. Atlas interviewed 10 Committee members, organizational representatives, and individuals heavily involved in the condition recommendation process. Questions asked during the interviews addressed topics including the factors guiding the Committee; the relative importance of personal stories included in the nomination package and of the overall nomination package; the decision matrix; the condition review process; the importance of screening tests; the way in which the Committee evaluates state screening capabilities; the importance of sufficient, high quality and what constitutes quality data; whether an accumulation of evidence is sufficient or a "gold standard" study is required, the definition of treatment for the condition, the involvement of a variety of multidisciplinary teams and advocacy groups, and resources that should be available to nominators.

The Chair of the E&T reported that the interviews were conducted during the summer. The Subcommittee reviewed the draft document prepared by Atlas during its meeting the previous day. The Subcommittee believes that the document is a good start, but wanted to see interviews with advocates, nominators, and professionals affiliated with the nominations. Atlas will conduct these interviews in the next few weeks. Once Atlas' work ends at the end of the month, it will be submitted to the Subcommittee for next steps.

The Subcommittee will use the information provided by Atlas to develop the document. Six of the Subcommittee members have volunteered to work on the document. The Chair of the E&T anticipated that work on the document and discussions about it would continue through the fall of the year and that the Subcommittee would deliver a draft document to the Committee for review in January 2014.

Priority C: Track, provide input on, and facilitate integration of national education and training initiatives.

The Subcommittee is working to identify one heritable condition that is not included in the RUSP and for which screening and treatment would occur later in child development and to identify the major education and training needs associated with the condition. This effort focuses on the Committee's mission focused on children.

In January, the Subcommittee selected fragile X syndrome, long QT syndrome, and Wilson's disease as exemplar conditions that would help facilitate the Subcommittee's discussion in this area. Each condition has been or will be presented at consecutive Subcommittee meetings. The Chair of the E&T anticipated reporting to the Committee on this effort in May 2014.

Questions asked by the Subcommittee concerning each condition address the typical pattern of identification of children with this condition, problems with the current pattern of identification and whether earlier identification would ameliorate these problems, the feasibility of population screening after the newborn period, the best-case scenario for later identification absent population screening, the level of effort required to substantially change the current paradigm, and the stakeholder groups that should be engaged in any discussions concerning changes in practice.

The E&T Co-Chair presented long QT syndrome to the Subcommittee. The condition is an inherited/genetic channelopathy identified by abnormal QT interval prolongation on electrocariography (ECG). The condition results in an increased propensity for a variety of outcomes, including sudden arrhythmic death. There are at least five genes that make up the classic forms of the condition with more than 300 different, related mutations. The condition

affects approximately one in 5,000 individuals and presents in a variety of ways. Treatments include prophylactic beta-blockers implantable cardioverter-defibrillators as secondary preventive measures. Long QT syndrome is typically identified through ECG and clinical history. Genetic testing is currently used primarily for research purposes, not clinical identification. Currently, the first presentation of this condition can be sudden death (no previous presenting symptoms). Population screening outside of the newborn period would be feasible/desirable if the diagnosis were predictive of clinical severity; in this case the presence of the genetic abnormality does mean that an individual has the disease. Absent population screen, systematic screening for symptoms and/or assessment of family history could be included in clinical guidelines. The E&T Co-Chair believed that it would take heroic efforts to change the current paradigm due to the challenges associated with the diagnosis and the uncertain future presentation. Stakeholder groups that should be included in any discussion of alteration of practice include cardiologists, geneticists, primary care physicians, and patients and families.

The E&T Chair indicated that this project will be a challenge. Currently, the Committee is making recommendations concerning the RUSP. He did not think that conditions such as the three under discussion would follow the same pathway. Instead, practice guidelines might be a more appropriate way to implement these types of screening.

Committee Discussion:

- A Committee member suggested that setting up a work group within the Committee might be one way to address the ethical and legal issues associated with these types of conditions as well as the common issues these conditions share with carrier testing. The E&T Co-chair indicated that she had served on a work group looking at carrier screening and suggested that any new work group pick up where that on left off.
- With regard to why NBS could not be performed for conditions meeting the NBS criteria, the E&T Chair noted that the treatment for fragile X would not meet the standard for treatment (i.e., clear evidence that identifying a baby with the condition would dramatically change the developmental trajectory). Clinical trials are ongoing, and medications for children over age five with fragile X could benefit from medications that are more disease-specific. The question is whether it would be beneficial to identify the condition earlier than it is currently.
- It was stated that the evidence process would not change, although some of the questions might be targeted differently.
- A Committee member pointed out that a distinction needs to be made between clinical practice recommendations and population-based screening involving public health entities. Some clinical practices, like the Bright Futures recommendations, include things that are listed as population screening.
- Another Committee advocated against relaxing standards (e.g. test specificity and sensitivity) when dealing with these types of conditions.
- A Committee member pointed out that many centers routinely offer fragile X carrier testing to all pregnant women.
- In response to a question from a member of the public, the E&T Chair indicated that the Subcommittee would have purview over information provided by the birthing hospital concerning NBS although it is not currently working on anything in this area. An organizational representative reported on the Genetic Alliance's training efforts, including those for nurse midwives. The organization works to provide education in the places NBS occurs and where people would be seeking information.
- An organizational representative indicated that the Save Babies through Screening Foundation markets its educational materials through professional associations and to those involved in perinatal care.
- The E&T Chair believed that Committee should consider its role in developing or influencing practice guidelines.
- The E&T Co-chair indicated that long QT syndrome is problematic for NBS because of the current screening and diagnostic algorithms (e.g., children could have ECG findings and a negative genetic test).

- A Committee member questioned whether the current makeup of the Committee supports addressing screening in older children. However, the methodologies it has developed could be helpful to other groups and should be published.

C. Subcommittee on Follow-Up and Treatment

The Chair of the Follow-Up and Treatment Subcommittee's (FU&T) reviewed the charter, which calls for it to:

- Identify barriers to post-screening implementation and short- and long-term follow-up, including treatment, relevant to NBS results;
- Develop recommendations for overcoming identified barriers to improve implementation and short- and long-term follow-up, including treatment, relevant to NBS results; and
- Offer guidance on the responsibility for post-screening implementation and short- and long-term follow-up, including treatment, relevant to NBS.

Priority A: Screening Program Implementation

The FU&T Co-chair reviewed the current status and recent changes to the paper titled "Some Lessons Learned from Early Hearing Detection Intervention (EDHI) that May Be Applicable to CCHD Screening." Highlights of the paper since the last Committee meeting include:

- Lessons learned:
    - The paper discusses challenges associated with point-of-care screening. State EDHI and NBS programs are often not well-integrated. Screening results might not all be available from a single source. There are also advantages to being able to include blood spot screening, hearing screening, and CCHD screening under a single program.
    - State health departments should play a leadership role in implementing electronic data systems utilizing standards-based messaging to reduce errors and enhance the timeliness of data reporting. The document describes how well states are doing this regard and identifies examples of this working well.
    - Screening programs should require child-level data for quality improvement purposes. Without individual data, it is difficult to ensure that everyone has been screened.
    - Appropriate federal and state support will be needed to develop, implement, and maintain CCHD screening systems. This includes funding and technical assistance

The FU&T Co-chair indicated that some states received grants to implement CCHD screening. He noted that it would be helpful to determine whether they are learning or implementing these lessons.

The FU&T Co-chair indicated that Subcommittee views the paper as a commentary that could be published in a journal as an editorial. He also stressed that the lessons identified from the EHDI experience could be applied to other point-of-care screenings.

Priority B: the roles and responsibilities with LTFU

Currently there is no specific projects active.

Priority C: A Framework for Assessing Outcomes from NBS: Do We Know If We Are Achieving the Promise of NBS?

The Chair of the FU&T reported that the Committee had originally envisioned a follow-up project on the implementation of CCHD screening. However, there are current HRSA projects looking

into this. One alternative might be to look at best practices for point-of-care screening and how the data is managed after the screening.

With regard to Priority C, The Chair of the FU&T stressed that the Subcommittee is not duplicating other efforts within HHS. The goal is to learn what is actually taking place. Work in this area focuses on developing key questions, understanding data sources, and identifying gaps. The Subcommittee will develop a framework to address these items and use sickle cell disease as an exemplar to test the framework. The Subcommittee has further developed ideas for using other disorders to test the framework, with the ultimate goal of developing a framework that can be applied to any disorder.

The Subcommittee has moved beyond the draft that the Committee has seen. The latest draft includes many revisions related to systems and quality improvement. The draft focuses on harmonization and avoidance of duplication. Determining the type of data that should be collected, the outcomes of LTFU, and which activities and actions after NBS are making a difference for patients.

The Chair of the FU&T indicated that the Subcommittee would appreciate feedback from the Committee members, particularly with regard to the types of data that should be collected. The Subcommittee has just established a work group to test the framework using another condition, such as phenylketonuria (PKU), to identify problems with the framework. There is much experience with PKU, but little formal data collection. Another possibility is to work with the cystic fibrosis (CF) community to determine whether the framework would work for this condition. Since there are no representatives from the CF community on the Subcommittee, there are concerns about sharing this information with individuals outside of the Subcommittee. The Chair of the FU&T indicated that the subcommittee members believe that this work is moving in the right direction.

The FDA is in the process of publishing new guidance on medical foods.

For the future, The Chair of the FU&T anticipated completing the EHDI white paper; completing the framework and, possibly, convening a meeting of stakeholders to discuss its utilization; and possibly working on a project to understand gaps or obstacles to services for children with hereditary disease. Other ideas for future work include looking at ways to envision and implement team health care for children with heritable disorders based on lessons learned from those providing care to individuals with non-heritable disorders and looking at how the delivery system affect care for heritable disorders (e.g., how accountable care organizations and capitation interacts with the medical home and specialists in the care of children with heritable disorders).

Committee Discussion:

- A Committee member expressed concerns that some of the points in the EHDI paper might get lost if the paper continues with its narrow focus on EDHI instead of NBS in general. Also, the points about the need for individual-level data should be expanded. Another Committee member agreed that the document should include more focus on the applicability of the lessons learned to NBS in general.

VII. Public Comment

Sarah Wilkerson, Board Member, Save Babies through Screening Foundation: Ms. Wilkerson advocated for the creation of guidelines for the timely testing of NBS samples to prevent newborn deaths such as those of her son, who died as a result of MCADD one day before his NBS test results were available. She recommended requiring hospitals to take the initial blood sample within 24 to 48 hours of life; prohibit the use of the U.S. Postal Service for delivering samples and use a courier service instead; prohibit batching of samples; and encourage labs to remain open on Saturdays, possibly by modifying work schedules to ensure continuous staffing.

Dr. Amber Salzman, President, Stop ALD Foundation: Dr. Salzman updated the Committee on NBS for adrenoleukodystrophy (ALD) in hopes of moving the review process forward. After reviewing past activities supporting the review process, she reported that 75,000 samples have been screened and analyzed as part of the Mayo biochemical genetics laboratory's pilot project. Ten of these samples were submitted for molecular testing, and four samples were found to be positive for a mutation in the gene responsible for ALD. She stressed that there is a reliable approach to conducting biochemical screening of blood spots, mechanisms are in place to do molecular screening of positive samples, and published studies confirm the need for early identification of affected children in order for treatment to be effective. Dr. Salzman asked for guidance on how to best work with the Committee to move the review of ALD forward in an expeditious manner.

Committee Discussion:

- An organizational representative noted that APHL is beginning a project with the CDC to study the effect of the recently released MMWR guidelines for biochemical genetic testing, which include aspects for this type of testing that is done by NBS laboratories. The guidelines address reliance on the Postal Service. The project will provide an opportunity to learn more about whether and how laboratories use the guidelines to address delivery of samples.
- The Committee members agreed to task the Laboratory Standards and Procedures Subcommittee with looking into issues related to the timely handling of samples and whether the Committee should make recommendations on this issue.

VIII. Update on MPS 1 Evidence Review

Alex Kemper. M.D., M.P.H., M.S.
Condition Review Workgroup
Associate Professor
Department of Pediatrics
Duke University
Durham, NC

The presentation began with a discussion of the revised version of the conceptual framework for assessing NBS before moving on to an update on the Condition Review Workgroup's (CRW) work on the MPS I condition review.

Revised Conceptual Framework of NBS Impact
The model used by the CRW for all of its previous reviews is one that has been thoroughly reviewed and is also used by the U.S. Preventative Services Task Force. Because the model does not address issues such as public health impact that the CRW includes in its condition review process, the workgroup believed that now would be a good time to revisit the model. The key questions addressed by the old model address very high-level issues and do not get at the nuances that need to be taken into account during the review process.

The new framework is divided into two parts that address the process of screening and diagnosis and what happens after a diagnosis is made. The model compares diagnosis by NBS screening and follow up to diagnosis based on usual care. NBS shortens the period of being undiagnosed and speeds the process of diagnosis and confirmation. The model illustrates the process of diagnosis and care based on NBS screening, identifies where it intersects and aligns with diagnosis by usual care, and shows the different outcomes based on NBS and follow up testing and treatment. With regard to outcomes, the model includes intermediate measures, such as biomarkers or functional measures; primary patient-centric health outcomes; and secondary outcomes. The model also addresses the assessment of benefits and harms of screening and short-term follow up and with treatment and long-term follow up. It also looks at how all of these elements fit within the larger health care system. Each of the elements of the model is tied to one of 10 key topic questions.

Key Topic Question 1: Usual Care and Course
This area encompasses the incidence of clinically detected disease in the United States, the distribution of the disease in its various forms, incidence of pseudodeficiency, and the average age of symptom onset, diagnosis, and treatment for the disease. These questions are designed to provide a sense of what generally happens in the course of clinical detection for the identified condition.

Key Topic Question 2: Screening and Short-Term Follow Up
Issues covered by this topic area include analytic markers; screening tests that can be used to find these markers; validity of the screening tests; clinical validity of available screening test algorithms in dried blood spots; the positive predictive value of NBS for the condition; benefits of early treatment; the ability of the screening to predict the form of the disease, carrier status, or pseudodeficiency; existence of prospective evaluation of the screening, and the availability of quality assurance and proficiency testing for screening laboratories. Dr. Kemper noted that the revised model addresses aspects of screening that might be considered purely as public health impact assessment, such as laboratory quality assurance, much earlier in the process.

Key Topic Question 3: Diagnosis
Questions include in this topic area relate to the case definition; approaches available for diagnosing the condition in both newborns and in older children; the way in which different forms of the diseases, carrier status, and pseudodeficiency are identified; the agreement, or lack thereof, on diagnostic approaches; the availability of quality assurance programs for diagnostic laboratories; the time needed to make or rule out a diagnosis; and any other factors that might affect treatment plans or outcomes that need to be addressed during the diagnostic period. The model accommodates the possibility of things other than the targeted condition being identified during the screening and diagnosis process. This could include carrier status or other conditions.

Key Topic Question 4: Benefits and Harms of Screening and Diagnosis (unrelated to treatment)
The CRW decided to separate the screening and diagnosis processes to better assess and explain the relevant information. Issues include under this topic area include benefits to the child or family associated with pre-symptomatic identification of the condition other than timing of treatment; the extent to which NBS changes the observed incidence of the condition compared to clinical detection; physical and psychosocial harms associated with other screening outcomes, such as false positives or carrier status; whether screening could detect other conditions; harms associated with diagnosis or the diagnostic process; and strategies available to minimizes screening and diagnostic harms.

The new model includes consideration of benefits to the whole family, not just the child. Dr. Kemper noted that this might be beyond the elements that the Committee would like to consider as part of its review and welcomed input on its inclusion in the model.

Key Topic Question 5: Treatment and Long-Term Follow-Up
Topics included in this area include standard of care treatment strategies for the various forms of a condition and the clinical guidelines for long-term follow up.

Key Topic Question 6: Intermediate and Outcome Measures
Questions in this area relate to intermediate or proximal outcome measures, biomarkers, or functional tests could be used for monitoring or evaluating the disease status; whether interventions for the disease detected by NBS lead to improvement in intermediate measures compared to clinical detection; and the effect of age at treatment initiation on treatment or intermediate measures.

Key Topic Question 7: Primary Health Outcomes
It was noted that the line between intermediate and primary health outcomes can be blurry. The goal of the framework is to capture all of the outcomes. Topics covered in this area include the most important health outcomes related to treatment based on identification through NBS and through usual care, factors other than age of initiation that modify the effect of treatment on primary health outcomes, the strength of the of the association between intermediate measures and

primary outcomes, the association of the intermediate measures to the primary outcomes, and the factors that influence the association between intermediate measures and primary outcomes.

Key Topic Question 8: Secondary Outcomes
Issues addressed within this topic area include quality of life, over time, and the effects on the family or caregivers, over time, when a disease is identified through NBS or usual care.

Key Topic Question 9: Benefits and Harms Related to Treatment and Long-Term Follow Up
This topic area addresses questions such as whether intervention for a disease that is detected through NBS versus that detected through clinical detection lead to improvements in primary or secondary outcomes, whether strategies exist to improve benefits or decrease/delay harms, and whether improvements in a primary or secondary outcome for a condition lead to another outcome that could be considered a harm.

Key Topic Question 10: Health Care System
Questions that fall into this topic area relate to the number of infants projected to be affected by NBS for a particular condition, including those that require short- or long-term follow-up services; the resources required to ensure state readiness to and feasibility of adopting screening and follow-up services; the resources required to ensure the capacity of the health service delivery system for short- or long-term follow up resulting from an expansion of NBS; and the availability and accessibility of screening, diagnostic, and treatment services.

Committee Discussion (includes comments made during presentation):

- A recommendation was made to indicate that short-term follow up addresses the detection of pre-symptomatic disease. This recommendation was accepted.
- A Committee noted that there have been problems with the availability of reagents, and recommended that this issue be included under Topic Question 2. This recommendation was accepted.
- Concerning the consideration of benefits and harms of screening for the family, a Committee member indicated that it something that should be considered as part of the review.
- Regarding health care system and public health benefits and harms, such as cost to the health care system, it was indicated that this issue comes up in many of the topic areas but was identified as a separate question for purposes of generating the report.
- A Committee member recommended that more focus be placed on the public health aspects of the framework. The presenter welcomed any advice that Committee might have concerning this part of the framework. With regard to Topic Question 4, a Committee member recommended making it clear that the discussion is of the benefits and harms to the child and family. This recommendation was accepted.
- While it is important to address the benefits and harms to children, families, the public health system, states, schools, and other entities, a Committee member cautioned against trying to fit them all into a single score. There various aspects could be weighted in some way but needed to be distinguished.
- A Committee member stressed the importance of doing more conceptual work on the public health impacts part of the framework, especially with regard to cost or availability of a treatment network. In some ways, the recommendations can be used to force changes in the system.
- A Committee member believed that the harms from things such as false positives should be included in Topic Question 9.
- A Committee member noted that it is difficult to provide guidance to nominators when the framework changes; however, this approach provides more detailed and clearer guidelines. The new framework will affect the work of the Education and Training Subcommittee, specifically with regard to the guidance document. Adding a short paragraph explaining each Topic Question would be very helpful to nominators.
- A Committee member suggested that training for newly implemented screenings should be added to Topic Question 10.

- The public health impacts for states and national system are different. It was noted that it is not feasible to look at these issues in each state; therefore representative states would have to be used. It is important that the Committee understand the range of impacts.
- A Committee member pointed out that the health care system and public health are not the same thing. The health care system of the framework should address the health care system, the delivery system, the workforce, and the professions. It was agreed that subheadings in this area would be helpful.
- Should the Secretary recommend the inclusion of Pompe disease in the RUSP, the inclusion of MSP I will be much easier, as it shares the same platform as Pompe.
- The Committee members discussed the importance of the questions that area asked and how they are asked in developing the information required by the framework. One member recommended holding a full-day meeting with experts in the field to further develop the criteria regarding health care system impacts.

MPS I Condition Review

MPS I Technical Expert Panel (TEP) held its first teleconference on September 9. The purpose of the meeting was gain a better understanding of the condition, refine the case definition; review the usual care screening and diagnostic process; review treatments; including potential benefits and harms, and clinical care guidelines; and identify key informants and other sources of information.

MSP I is an autosomal recessive lysosomal storage disorder (LSD) caused by deficiency of enzyme α-L-iduronidase (IDUA). It is progressive and affects multiple systems. Traditionally, it has been classified into three syndromes (Hurler, Hurler-Scheie, and Scheie), but it reflects a spectrum with no clear delineation between forms. Hurler is the severe form of the disease; Hurler-Scheie and Scheie are the attenuated forms.

In the severe form, infants appear normal at birth and develop symptoms during their first year of life. It progresses rapidly, involves the central nervous system, and is marked by severe cognitive deficits and progressive skeletal dysplasia. Death generally occurs in early childhood due to cardiorespiratory failure and neurodegeneration.

The attenuated form has a more variable onset and severity. Symptoms usually appears before age five and the condition progresses more slowly and more variably than the severe form. There is great variability in life span, with death occurring in the twenties through normal lifespans. The attenuated form is difficult to diagnose.

The results of an epidemiologic study of a sample of 106,000 anonymous dried blood samples from California was shared with the Committee. The various forms of the disease cannot be distinguished based on enzyme levels. The study estimated the prevalence of MPS I is 1:36,000, with a positive predictive value of 33 percent. The estimated false positive rate is 1:18,000.

Genzyme maintains an MPS I registry and has agreed to work with the TEP to analyze the registry data to estimate the value of early detection. Based on the registry data, the median age of onset for the severed form is six months versus two and five years for the attenuated forms.

A description of the anticipated screening process was described. The process begins with NBS of a dried blood spot that measures IDUA enzyme activity. In cases of low IDUA, the first step would be confirmation of the low activity level; use of a glycosaminoglycan (GAG) test, either urine or serum, to identify pseudodeficiency or a false positive screen; and mutational analysis.

The primary treatment option is stem cell transplant. The treatment window for babies is up to three months of age. Enzyme replacement therapy (ERT) can be used for the attenuated forms. Because ERT does not cross the blood-brain barrier, it cannot be used for the severe form. ERT can be used prior to transplant to stabilize babies (studies in this area are ongoing). Successfully transplanted infants do not need to continue ERT. The FDA approved ERT treatment for the attenuated form and for the severe form in cases where transplant was declined in 2003. Treatment is for the full lifetime and involves weekly transfusions.

Experts hypothesize that earlier initiation of treatment of MPS I based on NBS would improve outcomes. Patients with the attenuated condition might be able to reduce their ERT dosage if they begin therapy earlier. It was anticipated that ERT would not begin until the appearance of symptoms.

The TEP has initiated the literature search for the condition and has identified approximately 2,000 publications related to MPS I. The TEP will also contact states involved with MPS I screening and conduct key informant interviews.

IX. Whole Genome Sequencing in Newborn Screening

Amy Brower, Ph.D.
Project Manager, NCC-LTFU
American College of Medical Genetics

Dr. Brower, project manager for the National Coordinating Center's Long-Term Follow-up (NCC-LTFU) project, presented in place of Dr. Watson, who was unable to attend. She provided an overview of the basics of genome sequencing, noting that there is no normal genome sequence. At the DNA sequence level, humans are very similar — 99.6% of the base pairs are identical from one person to another. Despite this similarity, any two individuals can still differ by 24 million base pairs, and this is where genomic sequencing is applied in the newborn period. Genomic testing will play a role across lifespans, from tests before pregnancy to estimate the likelihood that a child will have a genetic disease, to blood tests during the first days of life to identify treatable diseases that cause disabilities and deaths, to tests later in life to determine which drugs to choose or which treatments to applied to individual patients.

There have been rapid advances in sequencing technology. Classical sequencing provides approximately 1,000 pairs of DNA sequence, about 600 base pairs long, whereas next generation sequencing can provide approximately 100 billion pairs of DNA sequences. Presently, costs are close to $1,000 per exome and $5,000, per genome, for using next generation. A further development is exome sequencing, which examines only the protein coding region of the genome. During 2010, whole exome sequencing was used to identify a gene in a rare condition known as Miller's syndrome. Future developments include third generation sequencing, a single-strand sequencing that requires no amplification of the DNA. At this time, third generation sequencing has limited interpretation.

The Newborn Screening Translational Research Network (NBSTRN) is currently supporting advances in new technologies to newborn screening and genomics through (1) a workgroup exploring ethical, legal, and social implications (ELSI); (2) a virtual repository of dried blood spots (VRDBS); (3) an aggregation of clinical data through a longitudinal pediatric data resource (LPDR); and (4) finalization of harvest, an integration of clinical data in LPDR with new findings from the genomic sequencing. Both NBSTRN and ACMG are part of a clinically relevant variant resource (CRVR) project to catalog and create curation on genomic findings.

In addition, there are new, five-year NICHD/NHGRI Newborn Screening and Sequencing Grant Program. This joint program, between the National Institute of Child Health and Human Development and the National Human Genome Research Institute, contains three components: (1) genomic sequencing and analysis; (2) research related to patient care; and (3) ethical, legal, and social issues in the use of genomic information and the newborn period. Dr. Brower briefly review four grantees of this program and their work with newborn screening and genomic analysis.

Committee Discussion:

- In response to a Committee member's question, there are two grantees of NICHD/NHGRI program are working directly with their state health department.

- Another Committee member asked if grantees were validating results from the new technology. Answer: Analytical validation of next generation sequencing and whole genome sequencing is one of main components of this project.
- A Committee member expressed concern that the cost of whole genome sequencing may exceed what society can commit to population-wide newborn screening. Response: as the grantees go through their five-year studies, more will be learned about whole genome sequencing and its potential applicability to newborn screening. A Committee member from NIH added that the NICHD/NHGRI program is designed to be a pilot study, determining factors that may contribute to performing whole genome or whole exome analysis. A Committee member added that these studies are important in addressing questions on what filters should be used, and what public health implications may arise.

X. Open Discussion on Future Meeting Topics

Dr. Bocchini commented that a number of important discussions on future meeting topics were raised during the course of this second meeting, and asked members if there were any additional considerations.

XI. Adjournment

With no additional business to address, Dr. Bocchini adjourned the meeting at 2:47 p.m.