Advisory Committee on Heritable Disorders in Newborns and Children

Summary of First Meeting
May 11-12, 2015

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) was convened for its first meeting at 10:00 a.m. EDT on Monday, May 11, 2015. The meeting was adjourned at 11:50 a.m. EDT on Tuesday, May 12, 2015. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

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I. Administrative Business: May 11, 2015

A. Welcome and Roll Call

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

Debi Sarkar, M.P.H.
Designated Federal Official
Health Resources and Services Administration

Dr. Joseph Bocchini welcomed the Committee members and other participants to the first meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). He took the roll for the first day of the meeting.

Voting members present were:

- Dr. Don Bailey
- Dr. Bocchini
- Dr. Jeffrey Botkin
- Dr. Fred Lorey
- Dr. Dietrich Matern
- Dr. Stephen McDonough
- Dr. Alexis Thompson
- Ms. Andrea Williams.

Ex Officio Members present were:

- Agency for Healthcare Research and Quality: Dr. Denise Dougherty,
- Centers for Centers for Disease Control and Prevention: Dr. Carla Cuthbert
- Food and Drug Administration: Dr. Kellie Kelm
- Health Resources and Services Administration: Dr. Michael Lu
- National Institutes of Health: Dr. Alan Guttmacher

Organizational Representatives participating in the meeting were:

- American Academy of Family Physicians (AAFP): Dr. Frederick Chen
- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- Association of Maternal and Child Health (AMCHP): Dr. Debbie Badawi
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State and Territorial Health Officials (ASTHO): Dr. Christopher Kus
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes: Ms. Ann Umemoto
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

Ms. Debi Sarkar, the Health Resources and Services Administration's (HRSA) Designated Federal Official (DFO), also greeted the participants and reviewed the process for participating in the webinar for Committee members, organizational representatives, and the public.

Dr. Bocchini reported that Dr. Charles Homer accepted the position of Deputy Assistant Secretary for Human Services Policy with the U.S. Department of Health and Human Services (HHS) and had to resign his position on the ACHDNC as a result. Dr. Bocchini, on behalf of the Committee, wished Dr. Homer continued success in his new position.

B. Approval of February 2015 Meeting Minutes

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

Dr. Bocchini indicated that the first order of business for the meeting was to close out the business of the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) by reviewing and voting on the meeting minutes for the February 2015 DACHNC meeting. The Committee members present unanimously approved the minutes.

C. Committee Correspondence

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

Dr. Bocchini reported that HHS Secretary Sylvia Mathews Burwell sent a letter to the Committee in March indicating her acceptance of its recommendation to facilitate a national dialogue among federal and state stakeholders on the benefits of measuring succinylacetone in dried blood spots (DBS) to improve the specificity of newborn screening (NBS) for tyrosinemia type 1. The Centers for Disease Control and Prevention (CDC) will help facilitate this process.

The Subcommittee also received a letter from Secretary Burwell indicating her acceptance of the Committee's recommendation to add Pompe disease to the Recommended Uniform Screening Panel (RUSP). The RUSP has been updated to reflect this change.

D. Advisory Committee Authorization

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

Dr. Bocchini explained that the Congressional reauthorization of the Newborn Screening Saves Lives Act, which became a law on December 18, 2014 created the ACHDNC. Since then, the charter for the ACHDNC has been created and signed by the Secretary.

New duties assigned to the Committee as part of the reauthorization include:

- Providing technical assistance, as appropriate, to individuals and organizations regarding the submission of nominations for the uniform screening panel (including assistance prior to the submission of nominations). This will increase the opportunities and responsibilities for the Committee to work with organizations and advocates to prepare conditions for nomination.
- Taking appropriate steps, at the Committee's discretion, to prepare for the review of nominations prior to their submission, including for conditions for which a screening method has been validated but for which other nomination criteria have not yet been met, in order to facilitate timely action.
- Including the cost of expansion of the RUSP in the public health impact analysis.
- Reviewing and voting on a condition within nine months of the date on which the ACHDNC referred the condition to the Condition Review Workgroup (CRW).
- Providing recommendations, advice, and information on activities necessary to achieve best practices in rapid diagnosis and appropriate treatment in the short term. This includes the timeliness of collection, delivery, receipt, and screening of specimens to be tested for heritable disorders in newborns to ensure rapid diagnosis and follow up.

Moving forward, Dr. Bocchini indicated that the Committee will need to reprioritize its work to address the new responsibilities and identified four priority areas:

- Determine the essential elements for nomination of a condition to meet the nine-month deadline.
- Support the efforts of the Pilot Study Workgroup's efforts to provide the Committee with the information needed before a condition can move forward to the CRW.
- Develop better ways to produce the cost and cost-effectiveness component. During the last meeting the Committee learned that a full cost and cost-effectiveness review would take between 12 and 18 months, which does not align with the new review timelines. The Committee needs to identify the essential elements that would make it possible to conduct this review within the nine-month review period.
- Timeliness of newborn screening from the collection of specimen through long-term follow-up on children identified with a condition via newborn screening.

In order to meet the nine-month requirement, the Committee will need to:

- Identify ways to assist the CRW.
- Identify the dataset necessary for the consideration of a nominated condition for evidence review. This will entail reviewing the entire nomination process, defining and standardizing the pilot study requirements, and defining the critical components of the cost analysis.
- Determine how to better provide technical assistance to potential nominators.

With regard to NBS timeliness from collection to follow-up, Dr. Bocchini reported that the Committee had already updated recommendations; encouraged states to benchmark progress, set goals, and report information; and sent a letter to the HHS Secretary concerning these activities. Moving forward, goals for the Committee include identifying the best ways to promulgate its recommendations; engaging hospitals, primary care physicians, providers, and specialists to meet these standards; and continuing to work with the March of Dimes and other stakeholders to move this effort forward as expeditiously as possible.

The Committee received authorization to meet four times per year. These meetings will be a mix of webinars and in-person events. There will be two more meetings in 2015: August 27-28 (webinar and in-person) and November 3-4 (webinar only). Meeting dates for 2016 are February 11-12, May 9-10, July 25-26, and November 3-4.

Section 12 of the Reauthorization requires that federally-funded research be considered as research on human subjects, which requires informed consent of the subject and eliminates the ability of institutional review boards (IRBs) to waive consent requirements for research on DBS until HHS updates the Common Rule. The update of the Common Rule is expected to occur within the next 18 months. The Committee needs to help define what constitutes research and help states address this requirement as they bring in new technologies and procedures and conduct quality control activities for their laboratories. As part of its activities related to this requirement, the Committee participated in a Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) stakeholder meeting in March; the Committee will also participate in a stakeholder meeting sponsored by APHL on June 1-2.

Committee Discussion:

- An organizational representative expressed his opinion that the in-person meetings are more productive and meaningful and advocated for scheduling more in-person meetings. Dr. Bocchini anticipated that the Committee would support such a change.

E. Nomination Process for Prospective Committee Members

Joseph A. Bocchini, Jr. M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics

Louisiana State University
Shreveport, LA

Dr. Bocchini reminded the participants that the schedule for changing Committee members was suspended due to the uncertainty of the lifespan of the DACHDNC. Now that the ACHDNC has been established, the rolling term limits for Committee members and organizational representatives have been re-established. Timelines for the changing of Committee members were developed based on when Committee members first joined and have been provided to the members. Timelines for rotating out organizational representatives will be determined in the near future.

The first new Committee members will join the ACHDNC in July 2016. Criteria for selection of new members includes expertise in medical, technical, or scientific professions with special expertise in heritable disorders or in providing screening, counseling, testing, or specialty services for newborns and children at risk for heritable disorders. Additionally, the Committee will seek out individuals who have expertise in ethics and have worked and published materials in the area of NBS.

A notice will be published in the *Federal Register* in June seeking nominations for membership in the Committee. Instructions for submitting nominations will be available on the ACHDNC website.

Committee Discussion:

- In response to a question about the timeline for replacing Dr. Homer, Dr. Bocchini indicated that he did not anticipate having a replacement in place until sometime in 2016.
- With regard to the process for identifying and approving new members, Ms. Sarkar explained that a notice would be placed in the *Federal Register* with a response period of 30-45 days. Applicants should provide a short summary concerning his/her ability to inform the Committee based on his/her expertise. There will be an internal HRSA review process that will include federal partners. The bulk of the review will be done by the HHS Secretary's office.

II. Impact of the Affordable Care Act Coverage Mandate on State Newborn Screening Programs

Julia Costich, J.D., Ph.D.
Professor, Department of Health Management and Policy
University of Kentucky College of Public Health
Lexington, KY

Dr. Julia Costich reported on the findings of a study of the effect of the coverage mandate in the Affordable Care Act (ACA) on state NBS programs. The findings were based on an extensive literature review that included websites and state laws, consultation with HRSA and CDC representatives, and interviews and conversations with state program leaders. The project focused on three main areas: states' adoption of the RUSP, payment models, and funding sources.

State Adoption of the RUSP
There is great variation in the ways in which states adopt the RUSP and in the ways they implement specific measures (implementation may require upfront expenses related to equipment and personnel training). The tests for severe combined immunodeficiency (SCID), hearing, and critical congenital heart disease (CCHD) are the most likely to be fully implemented and might be billed differently.

Payment Models
The most common payment model is one in which the birthing facility prepays the state agency for heel stick test kits and includes the cost in the newborn care charge. Under this model, the cost for CCHD and hearing are also included in the newborn care charge. A second common model is one in which the hospital receives the kits at no charge and pays the state agency when it submits them. In this scenario, hospitals

include the kit, CCHD, and hearing testing in the newborn care charge. Under a less common payment arrangement, states bill some, but not all, payers. There is often a specific arrangement with the state's Medicaid program for funding because it can be difficult to connect a child with his/her Medicaid identification number.

The fee that the state is allowed to charge for testing varies considerably. Fee revenue often goes back to the state's general fund. In some cases, there is a subaccount that provides accountability for these funds and directs them back to the laboratory. Other states require NBS programs to recompete for their own funds, which creates uncertainty with regard to program funding.

There are three states plus the District of Columbia that have no state fee. These programs use a combination of general fund monies and Title V support.

Payment issues identified by the study include:

- Repeat testing coverage is highly variable. It can be part of the overall testing fee, especially in those states that conduct two rounds of tests on a routine basis. In other states, repeat testing might be billed separately.
- Smaller facilities might contract with independent hearing test vendors that bill third-party payers or families directly. Dr. Costich reported that one such vendor has come under scrutiny for its collection practices.
- Parents may be unaware that they are entitled to coverage without cost sharing.
- The ACA mandate extends only to the screenings, not to other program costs, including medical food and formula.
- Families might wish to have the full slate of RUSP screenings. In cases where their respective states do not conduct screenings for the full panel, the tests should be available with no cost sharing. Dr. Costich highlighted the need for more public education on this issue.

Funding Sources

Dr. Costich shared the results of a 2006 survey published in *Pediatrics* that still represents a comprehensive picture of funding sources. In the survey, 90 percent of respondents indicated that fees collected from birthing centers were an important part of revenue. Other sources of income reported by respondents included federal pass-through programs such as Title V (61 percent), state general fund appropriations (33 percent), and direct Medicaid payments beyond routine newborn care (24 percent).

There were several common themes in the comments made by those Dr. Costich interviewed:

- States are not achieving the revenue that they could because they do not have the capacity for third-party billing. States often use a contracted billing service to perform this function.
- Medicaid identification numbers are not immediately available, which makes payment issues more complicated.
- Families might be billed separately for hearing testing without knowing that they are eligible for full coverage of these tests.
- The ACA mandate focuses on coverage for testing, but does not address follow-up care or capacity issues.

Committee Discussion:

- An organizational representative expressed her appreciation for the inclusion of the concerns about funding for long-term follow-up (LTFU) and the capacity of the program as a whole.
- A Committee member inquired about next steps for the ACHDNC related to the findings. Dr. Costich highlighted the importance of states' responsibility to provide parent education about these issues. She believed that the Committee could take on a role in helping states with their parent education efforts.

- In response to a question concerning the role that the HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE) might take in assisting states with their parent education efforts, Dr. Costich indicated that it was too early to speculate as the report had just been accepted by ASPE.
- Dr. Bocchini recommended that the Committee revisit this issue in three to six months, which would allow ASPE time to provide feedback and/or recommendations for which the group could provide support.
- An organizational representative asked whether any of the education materials provided to parents by the states that do not test for the full RUSP panel include information about which tests are not done by the state, how to access testing for conditions not tested by the state, and how costs for these tests are covered. Dr. Costich was unaware of such information being provided and conjectured that such counseling would most likely be provided on a case-by-case basis.
- The APHL representative indicated that in her state, Texas, billing advice concerning screening tests is provided to providers, not parents.
- An organizational representative indicated that the responses were very helpful and shed light on an area about which consumers might need more information.
- With regard to next steps, a Committee member noted that the main problems are state laboratories not having access to sufficient funding to provide optimal services and families having varied experiences with regard to coverage. He suggested that the Committee could identify this as a national problem and develop a set of recommendations for improving the situation. He also asked whether any quality analysis or evaluation of the funding models had been conducted. Dr. Costich indicated that there has been no in-depth analysis of the models.
- An organizational representative pointed out that the structure of each program determines how fees are allocated (e.g., the laboratory and follow-up functions fall within the same organizational unit and funding structure in some states while they exist separately in others). Because of this variation, it can be difficult to characterize the cost of NBS in each state. Dr. Costich replied that laboratory and point-of-care tests are often located within different organizational units and on databases that were not interoperable. Some states are moving toward combining reporting into a single document that provides an overview of all of the test results for an individual child. The movement toward unified reporting represents a best practice.
- With regard to family access to tests on the RUSP without out-of-pocket costs even if a state does not run a particular test, an organizational member noted that it would be interesting to see how this works out as it would involve insurance companies. It could also represent a major change for states if they have to pay for tests that they have not yet been able to bring onto their panels. Additionally, there is a bifurcation between lab-based services and follow-up, which can be further divided between short-term follow-up and LTFU. Short-term follow-up is often funded separately, and LTFU is almost always funded separately. It is important that follow-up not be ignored as the focus is shifted toward testing.

- Dr. Costich added that the complexity of determining what is and is not covered is exacerbated by the fact that some commercial plans do not currently fall under the ACA mandate (i.e., grandfathered plans). She anticipated that there would be near universal coverage unless an upcoming Supreme Court decision changes the ACA.

Dr. Bocchini recommended that the Committee review the full report prepared by Dr. Costich once it is released by ASPE and determine whether the Committee could study specific aspects of the report, use it to formulate best practices, or use the findings to better inform the Committee's requirements. The Committee could also use it as a jumping off point for further assessment of the ACA requirements and how they will affect families in those states that do not currently perform all of the tests on the RUSP.

III. Newborn Screening Saves Lives Reauthorization Act of 2014 – Informed Consent Amendment

Joseph A. Bocchini, Jr. M.D.
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Shreveport, LA

Dr. Bocchini introduced the portion of the meeting devoted to the Newborn Screening Saves Lives Reauthorization Act of 2014, which consisted of several presentations, discussion, and a vote on whether to support the recommendation made by the Secretary's Advisory Committee on Human Research Protections (SACHRP).

A. Overview of Newborn Screening Laboratory Processes and Quality Management

Scott Shone, Ph.D.
Program Manager
New Jersey Newborn Screening Laboratory

Dr. Scott Shone described the flow through an NBS laboratory and the ways in which quality is managed and monitored throughout the process. Laboratory analytic processes do not exist in a vacuum; quality impacts on one part of the system, such as the laboratory, directly affect other parts. Laboratory quality monitoring systems provide frameworks for the implementation of policies, processes, and procedures to ensure that all quality activities throughout the workflow are effective.

The "Newborn Screening: Toward a Uniform Screening Panel and System" report identified continuous quality improvement as one of the key components of NBS and affirmed that improvements result from careful and continuous monitoring of key steps throughout the process.

For the purposes of the discussion, Dr. Shone defined three key terms:

- Quality Assurance (QA): All of the planned and systematic activities implemented within the quality system and demonstrated, as needed, to provide adequate confidence and that an entity will fulfill requirements for quality.
- Quality Control (QC): The operational techniques and activities that are used to fulfill requirements for quality.
- Quality Indicators (QI): Metrics that give an indication of process or output quality that can be used to make comparisons across and within programs.

Dr. Shone equated quality with good laboratory practice. Quality is a regulatory requirement. The Clinical Laboratory Improvement Amendments (CLIA) define NBS as high-complexity testing; regulations covering such testing include requirements for proficiency testing, facility administration, quality systems throughout the entire process (e.g., pre-analytic, analytic, and post-analytic), and personnel qualifications. Many states also have their own regulatory bodies for clinical laboratories. National partners, such as the CDC's quality assurance program, provide QC material, proficiency testing materials, training, educational materials, and technical assistance. The Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) provides a data repository that aids in the monitoring of QIs and case definitions and evaluation over time. Additionally, NewSTEPs provides technical assistance and site visits to review quality processes that should be in place in laboratories and NBS programs. Laboratories use resources

available from a variety of sources (platform-specific and disorder-specific) to maintain and monitor quality. Dr. Shone encouraged the participants to review the CDC article, "Good Laboratory Practice for Biochemical Genetic Testing and Newborn Screening for Inherited Metabolic Disorders," which heavily influenced his comments.

The NBS system has three main components. The pre-analytic steps include test selection and ordering, collection of DBS specimens, handling and delivery, and receipt and accessioning into the laboratory. The analytic steps include preparation of the sample, test performance, monitoring and verification of test results, and documentation of test findings. Reporting results, measuring turnaround time, and verifying electronic data transfers are the steps in the post-analytic process.

Tests generally consist of kits that have gone through the Food and Drug Administration's regulatory process or of laboratory-developed or laboratory-modified tests. For the kits, laboratories must use DBS to verify the manufacturer's reported accuracy, precision, reportable range, and reference intervals.

Laboratory-developed tests require more robust validation including the establishment of the test's accuracy, precision, analytic sensitivity, analytic specificity, reportable range, reference intervals, and other performance characteristics. The use of DBS for this purpose is not research; instead it is a regulatory-required quality assurance process.

There are many QA challenges associated with the growth of disorder panels and the addition of rare disorders, including a need for positive samples for testing. Laboratories rely on each other to overcome these challenges.

The Clinical and Laboratory Standards Institute (CLSI) provides excellent standards for specimen collection. Laboratories monitor the quality of the actual specimens, time of collection (24-48 hours), and specimen receipt by the laboratory.

In New Jersey, the state NBS laboratory punches nine 96-well plates, which go to different testing units. The various units immediately begin screening using a kit or laboratory-developed test. Each test has its own robust quality monitoring process to ensure that results are consistently accurate. The purpose of QC is to detect immediate errors caused by test failure (e.g., failure of the test instrument or reagents used on the instrument, operator failure, environmental conditions, or other factors).

Measuring analytic quality is based on monitoring the performance of QC material (i.e., DBS). Kit manufacturers provide QC materials. QC materials are also available from outside vendors. Laboratories can develop and validate their own materials. At a minimum, controls that mimic the normal range and abnormal results must be assayed. Laboratories must establish their own ranges and ensure that the quality is consistent across all instruments on the same platform. Ranges must be re-established whenever a laboratory receives a new lot of reagents; as a result, laboratories often try to purchase as much reagent as possible within an expiration date to reduce lot-to-lot comparisons. Other events that might result in laboratories reviewing ranges include instrument maintenance, trends or shifts in results, or quality problems (e.g., a failed proficiency test). Programs need to run at least two levels to ensure quality, but most programs run more. Control materials are run with each assay of the newborn samples received. Acceptance criteria are based on Westgard rules or modified Westgard rules as well as patient values. Laboratories monitor plates, instrument-to-instrument comparisons, trends, and shifts. Over time, the hope is that a laboratory's QC will trend within two standard deviations above and below the mean on a Levey-Jennings plot. Trends can be caused by simple things, such as a dirty instrument, while persistence of QC issues could indicate reagent or test system failure. Laboratories might work with vendors, the CDC, and other laboratories to evaluate QC issues and to ensure comparability across states and across programs.

Dr. Shone indicated that SCID is one example of a success story. The test used for the condition is a laboratory-developed test used by New Jersey. It was developed through a collaborative effort with CDC and other states that used homemade DBS materials and the establishment of validation methods. The state

monitored quality indicators over the first few months of testing and discovered that the false positive rate was extremely high. Working with a consultant, the laboratory was able to resolve the issue. Since going live in June, the state has identified three children with SCID.

Dr. Shone also addressed proficiency testing. CLIA requires proficiency testing at least twice a year, and the CDC provides an external proficiency test (four challenges per year). In addition to external tests, states can do a specimen exchange to ensure compliance. States can also conduct internal proficiency testing. New Jersey uses leftover samples for this purpose.

With regard to post-analytic quality, Dr. Shone stated that turnaround time is a major quality indicator. Verification of electronic transfer of records and records and specimen retention are also important indicators.

Dr. Shone stressed that ensuring quality in one part of the system does not assure quality throughout the system.

B. Amendment 12 of the Newborn Screening Saves Lives Reauthorization Act of 2014: Landscape of Potential Implications

Michelle Huckaby Lewis, M.D., J.D.
Research Scholar
Berman Institute of Bioethics
Johns Hopkins University
Baltimore, MD

Dr. Michelle Huckaby Lewis discussed the background of the Informed Consent Amendment and its potential legal ramifications.

In order to ensure that they have enough blood to complete NBS testing, states collect more blood than is needed for screening, which results in leftover blood. States can use this blood for a variety of purposes including retesting the sample, quality improvement activities, forensic uses, and biomedical and public health research.

The controversy surrounding dried blood spots (DBS) has centered around parents being poorly informed about the retention and use of these samples. Until recently, under the Common Rule, research conducted using de-identified DBS was not considered human subjects research and did not require parental consent. In the past few years, privacy advocates have objected to the use of these samples in research without parental consent. Litigation in Texas, Minnesota, and Indiana resulted in the destruction of millions of DBS samples.

Bearder v. Minnesota
In 2009, the Minnesota NBS statute required that parents be informed that samples could be used for research and allowed them to opt out of having their children's samples used for this purpose. In that same year, nine families sued the Minnesota Department of Health claiming that the state's practice of retaining extra DBS samples unless parents opted out violated the genetic privacy provisions of the Government Data Practices Act. They argued that the DBS samples and NBS test results constituted genetic information as defined by law and that the practice of keeping these samples without parental permission violated state law. In their complaint, the plaintiffs did not distinguish between QA activities and research. QA activities were included in the list of activities for which the state used residual DBS samples. With regard to research, the de-identification of the data did not ameliorate the plaintiffs' concerns. They argued that the Genetic Privacy Act provisions applied to de-identified samples, not just identifiable ones.

The Minnesota Supreme Court ruled in favor of the plaintiffs. The court found that the state NBS statute provided an express exception to the Genetic Privacy Act only to extent that the state was allowed to administer the tests by testing the samples, reporting the results, maintaining a registry of positive results,

and storing results as required by law. Informed consent would be required for any other use. This meant that QA activities were not permitted without parental consent.

In response to the decision, the state legislature passed a new law that provided for an opt-out for retention and use of residual DBS samples and information for program operations (including studies used for new tests). Minnesota law defines program operations as utilization of blood samples and test results for studies related to NBS. The law required explicit consent for other types of research or release to third parties.

Beleno v. Texas Department of State Health Services
Also in 2009, several Texas families brought a class action lawsuit claiming that the practice of retaining and using de-identified DBS samples without explicit parental consent violated constitutional privacy rights and the right to be free from search and seizure. At the time of the lawsuit, no consent was required for the use of the DBS samples and parents were not offered the option to refuse their use. After the lawsuit was filed, the legislature passed a law implementing an opt-out procedure.

The settlement of the case required the destruction of five million retained DBS samples. After the settlement was reached, it was reported that the Department of State Health Services (DSHS) had given samples to the U.S. Armed Forces Pathology Laboratory. The plaintiffs claimed that this information was withheld during the settlement negotiations and filed a second lawsuit.

The second lawsuit spurred an additional change in the law, which now requires specific consent. This lawsuit was determined to be moot because of the change in the law. Dr. Lewis indicated that the legal issues in this case were never adjudicated.

Doe v. Vanness
Indiana law states that waste blood specimens are specimens that have served their intended purposes and have been discarded or accumulated for discard. A provision of the law related to the state NBS program requires the state to develop a system for using waste blood specimens for epidemiologic survey and research purposes. Another provision allows for the release of information for any purpose directly connected with the administration of the NBS program. Additionally, the state is required to maintain information about NBS positive test results and maintain a registry of positive cases for the purposes of service delivery and program administration. In summary, state law addresses the retention of information, use of information, retention of DBS waste specimens, and use of DBS samples.

Beginning in June 2013, parents of newborns must indicate whether their newborns' DBS can be made available for medical research purposes. If parents choose to have their child's sample saved, it will be stored and used for medical research (as de-identified data) for a period of three years before being destroyed. If parents do not want their samples kept for research, the state retains the sample for six months to ensure that further screening is not required before it is destroyed. Additionally, parents whose children were born before June 1, 2013, can request that their DBS samples be destroyed.

In June 2014, media reports of Indiana's practice of storing DBS samples without consent implied that the state was storing DBS samples at undisclosed locations. In September of that year, a class action lawsuit was filed alleging that DBS samples for babies born before June 1, 2014, were stored at an undisclosed location and that their parents were not informed of the state's intent to keep the leftover blood. The plaintiffs claimed that the state violated the right to be free from unreasonable search and seizure and the right to privacy.

The plaintiffs sought an order to destroy existing samples. Recently, the court granted state's motion to dismiss the case. Dr. Lewis indicated that the plaintiffs plan to appeal the ruling.

All three cases were based on privacy rights and addressed autonomy issues. In these cases, additional practices were viewed as objectionable (e.g., financial transactions were viewed as attempts to sell the

samples). Additionally, some uses that are viewed as standard practice within the NBS community could be viewed as objectionable by members of the public. Moving forward, it is important to clarify the definitions of research, public health practices, and program operations and administration.

Amendment 12
Amendment 12 states that federally-funded research conducted with DBS samples is considered human subjects research until updates to the Common Rule are promulgated.

Newborn Screening Translational Research Network
The Newborn Screening Translational Research Network (NBSTRN) is an NICHD-funded project tasked with promoting NBS research and building a research infrastructure. One of the tools created by NBSTRN is a virtual repository of DBS (VRDBS). The VRDBS is an open-sourced, web-based tool that enables approved NBS researchers to search more than 2.9 million DBS samples from participating states and identify the samples that are potentially available for NBS research. The goal of the VRDBS is to facilitate communications with state NBS programs. It allows states to manage these issues in a centralized fashion. Currently, four state participate in the program: California, Iowa, Michigan, and New York. Michigan is the only participating state that requires consent to use the samples.

With regard to the implications of Amendment 12 on the VRDBS, Dr. Lewis stated that none of the participating states planned to contribute samples collected after March 2015. It is not clear whether they are willing to contribute samples prior to that time. This means that it might not be possible to obtain a representative sample of a population at the current point in time. It might also be difficult, or in some cases impossible, to obtain sufficient samples for studies related to rare diseases. With regard to the work of the Committee, any conditions added to the RUSP after March 2015 will not have DBS annotated in the VRDBS.

State Laws Related to NBS Samples
Dr. Lewis briefly described a project she conducted to examine state laws related to DBS samples and consent issues. The project assessed the extent to which state laws addressed the retention and use of residual NBS samples. One goal of the project was to create an online toolkit for state policy makers that provides information on state statutes and regulations related to NBS sample retention and use. She anticipated that the toolkit would go live in June.

There is a wide variability in state policies regarding which party has the authority to determine what happens to leftover DBS samples, the circumstances under which they can be used, the purposes for which they can be used, and the amount of information provided to parents concerning the retention and use of their children's samples. Currently eight states have statutes or regulations related to parental consent to release DBS samples under certain circumstances.

Implications of Amendment 12
Dr. Lewis indicated that the potential implications for NBS research and other research that uses DBS samples are not clear. The definition of research in this context will have profound implications on the work that can be done using these samples. The permissibility of blanket consent will likely determine the future utility of resources such as the VRDBS. Amendment 12 could potentially limit research on rare conditions.

It is important that the new law not have a detrimental effect on state NBS programs. It is also important to consider the implications for DBS samples and the information derived from them, not just the samples themselves. There have been discussions about the broad issues related to consent in the NBS process and the timing of consent discussions with parents. There are more ways to protect research participants and their families than informed consent. Governance is an important element of protecting these individuals; robust policies regarding access to samples and related information and the purposes for which they are used could help build trust in NBS programs and the research enterprise.

C. Summary of the Secretary's Advisory Committee on Human Research Protections Meeting on the Newborn Screening Informed Consent Amendment

Jeffrey Botkin, M.D., M.P.H.
SACHRP Committee Chair
Professor of Pediatrics and Medical Ethics
Associate Vice President for Research
University of Utah
Salt Lake City, UT

Dr. Botkin described the responsibilities, membership, and background of the SACHRP and discussed the group's recommendations concerning the informed consent amendment to the Newborn Screening Saves Lives Reauthorization Act.

SACHRP reports to the HHS Secretary and is staffed through the Office of Human Research Protections (OHRP). The membership includes representatives from academia, pharmacy professions, the legal field, industry, and lay people. Initially, the committee was under the umbrella of the National Institutes of Health's (NIH) Office of Protection from Research Risks, which was an internal NIH office. It was moved out from under NIH in 2000. The National Human Research Protections Advisory Committee was the immediate predecessor group (2000-2002) to the SACHRP (2003 – present).

SACHRP is charged with determining how regulations could be reinterpreted to help strengthen any perceived gaps in human research protections and with identifying ways to reduce the regulatory burdens on the conduct of human research.

SACHRP made several recommendations to the HHS Secretary during its March meeting. The Committee has not yet received a response to the recommendations. OHRP will also make its own considerations about how the recommendations might move forward. In formulating the recommendations, SACHRP tried to balance its strong support for consent and parental engagement with the importance of promoting research for the benefit of children. The original research regulations were not written with research using residual clinical samples in mind. For the purposes of the recommendation, the SACHRP used the definition of research contained in the regulation, which defines research as systematic investigation, including research development, testing, and evaluation, designed to developed or contribute to generalizable knowledge.

The SACHRP recommended that:

- OHRP rapidly disseminate guidance on Public Law 113-240 to the research community regarding its implementation.
- OHRP guidance reinforce the idea that institutions should continue to assess proposed activities to determine whether or not they represent research. SACHRP was concerned that the law could negatively affect QA activities.
- Guidance should make it clear that the requirements of Subsection (a) of the law only applies to HHS-funded research and does not affect other sources of funding. Dr. Botkin noted that many institutions will extend federal regulations to research that is funded by sources other than the federal government. The recommendation encourages OHRP to decline to enforce the regulations in the context of research that is not funded with federal monies, even if the institution has voluntarily extended federal requirement to such research.
- OHRP's 2008 Guidance on Engagement of Institutions in Human Subjects Research be revised to include scenarios for the collection of DBS. SACHRP was concerned that birthing centers would be considered to be engaged in research by virtue of their collection of NBS DBS samples. In general, institutions are considered to be engaged in research if they collect data about subjects, use private identifiable information, and, specifically, obtain informed consent of human subjects for research. SACHRP hopes that the regulation will be interpreted in such a way

as to prevent every birthing center from being considered to be engaged in research by virtue of having their nursery staff obtain permission for the research use of residual samples and prevent every nurse from being considered an investigator subject to the educational requirements for investigators.

- OHRP guidance encourage the de-identification of DBS used for research unless there is a clear justification to do otherwise. With the advent of the consent requirements, there is less incentive for researchers to use de-identified specimens.
- OHRP guidance should indicate that the expedited review categories may be used for HHS-funded research with newborn DBS. Expedited review is used for minimal risk research.
- OHRP guidance should emphasize that the consent process for DBS would be simplified if one-time permission is sought for broad future research use. Dr. Botkin indicated that this idea has been somewhat controversial within the ethics and regulatory communities with regard to biobanks. The concern is that if each investigator has to obtain consent for each sample for each project, research would no longer be practical.
- OHRP should consider developing an example of a broad consent for research use of newborn DBS as part of its guidance. Under the new law, there are eight elements of consent, none of which can be eliminated, revised, or simplified. OHRP has suggested that these eight elements have to be physically part of the signed consent form.
- OHRP guidance should emphasize the ability of IRBs to grant waivers of documentation of consent under §46.711(c)(2). Under this scenario, an IRB must find that there is no more than a minimal risk of harm and involves no procedures for which written consent is required outside of the research context.
- Caution should be taken in the application of exempt Category 4 to research involving DBS. There was some discussion concerning whether the exemption category in §46.101(b)(4) is precluded by Section 12 of the Reauthorization Act. This represents a possible loophole in the law, and SACHRP recommended caution in the use of this exemption category.

Committee Discussion:

- A participant asked about the normal process for obtaining DBS samples in the nursery, specifically whether hospital employees ask parents about the research issues and obtain documentation at the time of sampling. Based on his experience outside of the SACHRP process, Dr. Botkin indicated that there is a moderate amount of experience with the signed consent form process. The experiences in California and Michigan (BioTrust) indicate a significant decrease in the acquisition of samples. This is because nursery staff has limited time to engage families in this type of conversation, not because parents say no to the request. He anticipated that an informed consent process requiring a signature would have significant negative effects on research.
- An organizational representative observed that the lawsuits in this area were based on the DBS being identifiable because of the DNA they contain and asked whether OHRP has considered adding genomic or DNA data as an identifiable item. Such a move would mean that de-identified DBS would no longer be considered as de-identified. Dr. Botkin indicated that neither SACHRP nor OHRP has begun to address this issue. The definition of identifiability under the Common Rule provides a relatively low bar (i.e., information must not be readily identifiable to the investigator).
- The same organizational representative asked about definition of research as resulting in generalizable knowledge and its effect on projects such as the Pompe disease pilot study. Dr. Botkin indicated that he was unfamiliar with OHRP's reasoning concerning the Pompe study. He anticipated that decisions such as the one made concerning the Pompe study and its research context would not be routine. States might mandate certain tests and collect information along the way; this might be interpreted as a public health program for which states are collecting data as opposed to research. The line between information collection and research is a fine one.
- Dr. Botkin asked Dr. Shone about the effect of the new law on the existing robust quality systems that are in place, specifically whether he considers any of the work being done as research. Dr.

Schone indicated that for many of the things he discussed, there has been an effort to define them as regulatory-required QA processes rather than research. A small number of activities might fall under the definition of research because they are producing generalizable knowledge and would require consent. He hoped that by partnering with SACHRP and other organizations, there would be more knowledge brought to the discussion.

D. Texas Opt-In Methodology for Sample Storage and Research

Susan M. Tanksley, Ph.D.
Association of Public Health Laboratories
Manager, Laboratory Operations Unit
Texas Department of State Health Services
Austin, TX

Dr. Tanksley described the opt-in methodology for sample storage and research that has been used in Texas for the past several years.

NBS is the responsibility of DSHS in Texas. There are approximately 400,000 annual births in the state. Texas NBS is a two-screen process with the first specimens collected within 24-48 hours of life and the second specimen collected between one and two weeks of life. In 2014, the state laboratory in Austin screened approximately 780,000 specimens.

Prior to 2002, Texas stored DBS specimens for six months before discarding them. In 2002, the state began storing specimens indefinitely. The change was made in the hopes that research could be done using the data in the birth defects registry and the NBS data. There was no specific policy concerning the use of DBS. De-identified specimens were allowed to be used for external research use with approval of the DSHS IRB.

In May 2009, HB 1672 was signed into law. It allowed the use of residual NBS specimens for QA and QC purposes, quality improvement, and research use. The law included a disclosure requirement and allowed parents to request the destruction of their children's specimens. Unless parents opted out by requesting specimen destruction, samples would be stored for up to 25 years. De-identified specimens and data were approved for external research purposes.

After the passage of the law, DHSH adopted a strict policy for use of the specimens. The policy includes a table of uses with specific cross-references to the relevant statutory authority. It also includes a list of required approvals for each of the uses and describes the approval process. As a result, some requests can be approved based on the policy itself or on statutory authority while others may require additional levels of approval, up to the commissioner level.

In 2011, HB 411 changed the law by requiring written parental consent for the storage and use of newborn DBS. The consent card that parents must sign to opt in indicated that specimens can be stored for up to 25 years and can be used for external research if consent is provided. As a result of the change in the law, the state had to design new forms, new collection kits, and collection processes. Because of the new law, the destruction timeframes for the samples changed. Prior to HB 411, samples had to be destroyed within 60 days if parents opted out; after the change, destruction would occur within two years.

DSHS had several implementation goals. The chief goal for parents was to ensure that they understood the choices available to them. The state also put a priority on being sensitive to parent and patient privacy concerns and to improving educational efforts around NBS. The state also sought to help providers better understand the new legal requirements, to streamline the distribution of consent forms, and maximize the return rates of the forms. The NBS program worked to ensure that it complied with parental choices and the law, to make processing easier, to be able to document choices in the laboratory's information management system, and to collect just enough information to match forms to specimens.

Dr. Tanksley shared a copy of the new consent form with the participants. The information form, which was targeted toward a fifth-grade reading level, is printed in English and Spanish and is given to parents each time a sample is collected. It explains NBS, how to get results, and what happens to specimens after testing (i.e., explains the opt-in options). The opt-in portion of the form, the Parental Decision for Storage Form, focuses on the disclosures required by law. The current form does not meet all of the requirements for informed consent; the form is being rewritten to do so. Forms must be signed to be considered opt-in. If forms are unsigned, not filled out completely, or not received, they are considered to be a "no" to the opt-in.

In 2014, 45.14 percent of all specimens received included a valid decision form (this covered approximately 49 percent of all babies screened). Of the forms received, approximately 71 percent opted in to storage and residual use.

Factors considered by the DSHS as it implemented the program included the need for minimal legal requirements and no consequences for non-compliance for providers, concerns about lack of provider understanding of the requirements, and the disincentives to provider compliance. The agency also considered problems related to parents not receiving the forms, not receiving an explanation of the forms, or not understanding the ways in which forms can be returned.

Dr. Tanksley indicated that one of the state's priorities moving forward is the preservation of core program uses such as screening, QA/QC regulatory requirements, and program improvement.

E. Michigan Opt-In Methodology for Sample Storage and Research

Carrie Langbo, M.S., C.G.C.
BioTrust Coordinator
Michigan Newborn Screening Program

Ms. Carrie Langbo described the history of the Michigan BioTrust for Health and its current consent process.

The seeds for the BioTrust were planted in 2000 when the public health code was amended to allow the use of the residual NBS DBS in health research. The Governor's Commission on Genetic Privacy and Progress recommended long-term storage of these samples because of their potential future use in research. The public health code allows the Michigan Department of Health and Human Services (MDHHS) to set the retention period for the samples. Currently the samples are stored for an indefinite period. The code also requires that the NBS brochure must mention the use of DBS for research. The BioTrust was formally launched on June 1, 2009. The priorities for the BioTrust are preserving DBS and promoting their use for research purposes, increasing community awareness and engagement, and improving the decision-making process about the use of the samples once NBS is completed.

Michigan's collection of DBS consists of two sets. The first set is an archived pool of samples collected prior to the implementation of the consent process (samples collected between July 1984 and April 30, 2010). These samples are available for research approved through the BioTrust under a waiver of informed consent approved by the BioTrust IRB unless a parent or individual opts out. Parents and individuals can opt to have their samples destroyed or stored but not made available for research. The consented collection consists of samples collected between May 1, 2010, and the present day. These are approved for research use if the MDHHS has a consent on record. Together, the two sets include approximately five million samples. All of samples are coded, processed, and stored in the Michigan Neonatal Biobank in Detroit. The MDHHS retains one full spot from each sample for future need by the parent or child.

In order for DBS to be used for research, investigators must submit their protocols for review by the BioTrust's scientific advisory board as well as the MDHHS IRB. Once a protocol has been approved, the samples undergo a second coding and de-identification process. The number of research requests has increased since the establishment of the BioTrust. This year there has been a noticeable drop off in

requests. Most of the approved requests come from academia; only a small portion of the approved studies are federally-funded.

The state took the better part of a year to design the opt-in process and related materials. Materials were developed in conjunction with the BioTrust advisory board and were focus group tested. The state was also able to coordinate the development of the consent brochure and form with the NBS cards.

The state piloted the opt-in process in the late spring and early summer of 2010 in 11 hospitals. The goals of the pilot phase were to identify best practices before implementing the process statewide and to ensure that the process was the least burdensome for hospital staff and the most informative for parents. In most of the more than 650 patient encounters, the majority of parents were able to find answers to their questions in the consent brochure, and only a few required extra time to ask additional questions. The pilot study highlighted the need for a way to document parent refusals (without one there was no way to document that parents had even gone through the process).

Following the completion of the pilot phase, the BioTrust made some revisions to the brochure and fine-tuned the process and began implementing the program in anticipation of the October 1, 2010, deadline. As part of the implementation, the MDHHS Director wrote a letter to hospital chief executive officers encouraging them to participate (there was no legislative mandate for the opt-in process to take place in hospitals). The BioTrust worked with the NBS coordinators in 86 hospitals to enroll hospital staff in one of three training venues. Most staff (62 percent) enrolled in an online training module, a large minority (29 percent) participated in in-service training, and the balance viewed a webcast. Nurses received continuing education credits for participating. More than 650 nurses received training. Additionally, the program reached out to homebirth attendants who had submitted a newborn screening since 2008 to ensure that they were aware of the BioTrust and the consent process and that they could participate in the training and offer the process to their patients. After program initiation, the state provided an after-hours hotline to respond to questions.

Currently, the consent process and associated materials consist of a brochure and a declaration form, which is found in the NBS card. The consent brochure is used in conjunction with the declaration form. These materials were designed with the goal of making them easy to read, able to contain sufficient detail, and able to be used for education during the prenatal period.

Ms. Langbo indicated that it is important to consider the possibility of waiving or altering the requirements for documenting consent. Such a possibility would allow states to choose the most logistically feasible process for their respective programs.

As of the first quarter of 2015, the BioTrust is receiving approximately 84 percent of the consent forms for newborns (including both refusals and documented consents). Sixty-six percent of children born in this period have a consent on record. Of the remaining newborns, 18 percent have a refusal on record, and 16 percent have no decision on record (e.g., forms were incomplete or not returned); for these two categories, the DBS are retained but not made available for research.

Ms. Langbo identified several of the concerns that drove the development of the BioTrust opt-in methodology. Hospital engagement in research was one of the chief concerns. If individual IRBs determine that hospital staff are engaged in research because they collect consent, consent forms might have to be changed, the consent process will no longer be consistent across the state, and logistical barriers for departments of health that are responsible for maintaining the consent process will result. Several hospitals reviewed the process and determined that collection of consent did not constitute research since the MDHHS was listed as the responsible entity. Another concern was the importance of ensuring the integrity of NBS (the process could not delay NBS). The consent process helps parents distinguish between the clinical testing and the personal choice to participate in the BioTrust. Additionally, including the declaration form as part of the NBS card has played an important role in tracking and coding consent forms and matching them to specimens. Monitoring hospital performance is an important, ongoing process and helps ensure that parents are asked about consent and that hospitals receive on-going feedback and training.

California Consent Status

Following Ms. Langbo's presentation and the public comment period (see below), Dr. Lorey reported on the current situation regarding informed consent in California. When California conducted its mass spectrometry pilot study, it developed a consent form. In the end, only 50 percent of the children were tested, primarily because the hospitals refused to participate. For the SCID pilot, the state obtained a waiver of review from the IRB and tested everyone.

Currently in California, a bill, AB 170, includes a state version of Amendment 12. It proposes that all NBS tests have a signed consent and that all storage of DBS samples have a signed consent. There have been many accusations concerning lack of transparency, the biobank, and the process for destroying specimens. The author of this bill maintained that he and his wife were never informed about NBS or storage of specimens; however, the state provides this information in booklet form during the prenatal period and again in the hospital. A significant number of organizations joined together in a very short period of time to oppose the bill and swamped the legislator with comments explaining their opposition. They also attended a hearing on the bill and overwhelmed the meeting with their comments. After withdrawing the bill, the legislator replaced the signed consent requirement with a directive that the Department of Public Health draft a one-page explanation of NBS, how DBS are used, and how to opt-out. Parents would have to sign a form acknowledging that they received the information instead of signing a consent form.

Now that the signed consent has been removed from the bill, the March of Dimes has shifted its position from opposed to neutral; most of the other organizations remain opposed to the bill because of the misinformation included in it. Currently, the hospital association presents the strongest opposition because its members will be responsible for giving parents the form. Efforts to oppose the bill are ongoing.

IV. Public Comments

Dr. Martin Kharrazi, Independent Epidemiologist: Dr. Kharrazi spoke from the perspective of an epidemiologist with extensive experience conducting research involving newborn DBS and facilitating federal, state, and academic research using newborn DBS in California. He maintained that the informed consent requirement in the newborn screening legislation under discussion will result in many problems and costs and few, if any, benefits. The state's interest in preventing mental retardation, death, and other serious health consequences of genetic and other diseases in children through early identification through NBS takes precedence over parents. There are wide and important benefits of a population-representative biobank of newborn specimens and the dismantling of public health research resources should not be allowed. An opt-out provision is a balanced approach to maintaining privacy rights. Additionally, DBS can be used for unexpected needs, such as diagnosis following fatal disease. Neither broad nor specific informed consent guarantees privacy protections. Dr. Kharrazi was also concerned about the role of the IRB being usurped by the new law and about the cost to conduct appropriate education concerning consent issues. He asked the Committee to consider how a better federal law could be enacted that finds the right balance between protecting public, state, and parental interests.

V. Committee Discussion and Vote

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

Dr. Bocchini opened the meeting up for discussion of the presentations concerning the informed consent amendment to the Newborn Screening Saves Lives Reauthorization Act before calling for a vote on proposed ACHDNC recommendations concerning research uses of newborn DBS.

Committee Discussion:

- An organizational representative asked about how well the consented repositories in Texas and Michigan represented the state populations. Ms. Langbo indicated that preliminary assessments indicate some slight differences in comparison to the general population. The number of Black and Arabic infants in the consented pool is slightly lower than the general population, and the number of White infants is slightly higher. The reasons behind these differences are not yet clear.
- The importance of never defining QC activities as research was raised by an organizational representative. Defining QC activities as research would cripple laboratories' ability to deliver quality newborn screens. QC must be allowed without consent. Dr. Tanksley added that there is no intent within QA/QC activities for generalizable knowledge. These activities are necessary to ensure that tests work accurately and to determine performance specifications. Laboratories are required by federal law to adhere to QA/QC standards in order to continue testing.
- In response to a question about the number of specimens needed to conduct quality management activities, Dr. Tanksley indicated that samples must be representative and free from bias. The number of specimens required would depend on the size of the population, the condition being screened, and the test itself. The fewer samples used in establishing test criteria, the more likely it is that there will be bias in the reference ranges moving forward. These ranges can be refined as more data is collected. Dr. Shone stressed that monitoring quality and maintaining robust systems is an ongoing process. When doing population-based screening, it is imperative that the quality is based on that population.
- A Committee member noted the need for a review of research that has been done using DBS. He asked about the Texas experience concerning research with its DBS and any possible role the Committee might play in encouraging research. Dr. Tanksley replied that the number of requests from researchers is increasing. Texas is making sure it is following the current law as it responds to requests. The state has adopted the federal IRB regulations and DSHS has requested an exemption from this policy until the Common Law is revised. She agreed that a compilation of DBS research would be helpful, especially for research used for purposes other than to support implementation of new screenings.
- With regard to developing a list of NBS accomplishments as a result of the use of residual DBS, Dr. Watson agreed that such a list would be valuable and indicated that NBSTRN has considered looking at gaps in research. Dr. Guttmacher also agreed and noted that much of the DBS research was not federally-funded.
- Dr. Bocchini suggested that compilation of such a list would be an appropriate task for the Committee. The timeline for completing the project would be relatively short. Dr. Lewis pointed out that some states list the types of projects that have been approved. One paper pointed out the difficulties caused by the disparity in state laws regarding the use of residual DBS.
- A Committee member expressed interest in the costs associated with establishing Michigan's biobank and with Texas' consent program. He also stressed that without access to residual DBS without consent, there would probably be no NBS screening apart from phenylketonuria.
- An organizational representative noted that the move toward informed consent for the use of residual DBS was driven by the public, not by the groups represented at the meeting. The public health communications aspect of this issue needs to be part of the discussion. Messaging that helps people understand the issues needs to be developed. Unfortunately, public engagement tends to be underfunded or unfunded.

Committee Vote

Dr. Bocchini asked the Committee to vote on the first recommendation:

> **Recommendation 1**: The Secretary of HHS should adopt the "SACHRP Recommendations Regarding Research Uses of Newborn Dried Bloodspots and the Newborn Screening Saves Lives Reauthorization Act of 2014."

Dr. McDonough made a motion to accept the recommendation. Dr. Thompson seconded the motion.

Dr. Lorey indicated his wholehearted support of the recommendation; he also expressed his concern that asking the HHS Secretary to work with the states and IRBs would not solve the problem. State legislatures do not understand that the IRBs are the organizations that are supposed to make decisions about issues such as consent. Dr. Matern stated that the recommendation concerns the amendment to the Reauthorization Act, which addresses consenting, not the laws that are going into effect in the states. He suggested that the Committee recommend the repeal of that part of the Reauthorization Act. Dr. Botkin, speaking in his role as a SACHRP member, noted that secondary use of clinical samples for research use is widespread in the biomedical enterprise. SACHRP was concerned about having a legislative change to this particular domain without sufficient discussion. It would be challenging for a member of Congress to propose repealing the informed consent as it would seem to oppose parental choice. The Common Rule will have a Notice of Proposed Rule Making (NPRM) within a few months; this will provide an opportunity to change federal regulations in a way that helps promote valuable NBS research using DBS. The ACHDNC should take a close look at the portions of the NPRM related to DBS and submit recommendations concerning the ways the new rules can support this important area.

Dr. Greene expressed her hope that the Committee would approve the recommendation concerning the SACHRP's recommendations. She also recommended that the second recommendation include a statement about the paralyzing effect of not allowing laboratories to use residual DBS for quality purposes and the direct effect it would have on babies.

VOTE: Dr. Bocchini called for a vote on the first recommendation concerning adoption of the SACHRP recommendations. Dr. Botkin recused himself from the vote based on his affiliation with SACHRP. The motion passed with all of the remaining 10 Committee members present voting affirmatively.

As background for the second vote, Dr. Bocchini explained that the final four recommendations were developed as a result of the Committee's meetings with stakeholders and internal Committee discussions. He anticipated that these recommendations would be sent to the HHS Secretary in a letter.

> **Recommendation 2**: The Secretary of HHS should work with States to develop guidance for Institutional Review Boards that distinguish between research and non-research in the context of required, routine newborn screening program activities such as quality assurance, quality improvement, and method development for new screening conditions.
>
> **Recommendation 3**: The Secretary of HHS should work with States to develop guidance for Institutional Review Boards that identifies appropriate models for broad or blanket informed consent for using residual dried blood spots to (1) develop new methods or (2) perform newborn screening research.
>
> **Recommendation 4**: The Secretary of HHS should work with States to develop guidance for Institutional Review Boards that identifies appropriate models for broad or blanket informed consent for States that choose to store residual dried blood spots for future research purposes.
>
> **Recommendation 5**: The Secretary of HHS should create and distribute communication materials on the importance of newborn screening and options to participate in research to professional organizations associated with obstetricians, nurses, midwives, and other health care workers who care for pregnant women and the public.

Dr. Bocchini added that the letter transmitting these recommendations would state that states should be encouraged to monitor whether requiring informed consent for NBS samples for future research negatively affects clinical NBS rates. States should also be encouraged to monitor who does and does not consent in order to determine what types of materials are needed to ensure that the overall NBS rate remains high and

to determine whether or not the stored NBS samples reflect the U.S. newborn population. The letter will also emphasize the need for timely action on these recommendations.

Dr. McDonough made a motion to approve the recommendations. Dr. Thompson seconded the motion. With regard to the letter, Ms. Williams suggested that the letter should ask that states monitor how informed consent affects research without assuming it would be a negative effect. Additionally, there should be a statement that states need to ensure that parents receive education about DBS research prior to making their decisions. The recommendation should incorporate the broader parent education effort. Dr. Bocchini indicated that her comments could be incorporated into the recommendations and letter.

Dr. Bailey stated that there is a need for evidence-based practices based on a national study that would help parents better understand what they are consenting to and that would maximize uptake rates in an appropriate way. Dr. Bocchini agreed that these suggestions were reasonable and should be incorporated into the recommendations.

Dr. Tanksley stated that APHL will host a national conversation on NBS research and informed consent on June 1-2. Representatives from all of the states have been invited to attend. The event will include an opportunity to outline the routine uses of NBS DBS and define whether these uses constitute research. The meeting will also address broad consent issues. She offered to report back on the meeting outcomes during the Committee's August meeting. Dr. Bocchini recommended that the Committee's recommendations include the findings of the APHL meeting and similar meetings of other groups. Additionally, the recommendations should be fleshed out to include some of the information from the presentations concerning laboratory activities that are not research.

Dr. Greene also believed that the Committee's recommendations should include examples of activities that are not research and as well as a strong statement concerning the potential crippling of state NBS programs if states are not issued guidance concerning what is not research.

Dr. Botkin suggested that a new recommendation be added that encourages the HHS Secretary to consider mechanisms to promote federally-funded biomedical research using DBS. Dr. McDonough agreed to incorporate this recommendation in his motion to approve the proposed recommendations. Dr. Thompson also agreed to incorporate it into her second.

Dr. Matern suggested that Recommendation 4 concerning models for broad or blanket consent for DBS storage for future research include language concerning cost-effectiveness (e.g., change "appropriate models" to "appropriate, cost-effective models"). Dr. Bocchini asked whether adding Dr. Bailey's suggestion about mentioning evidence-based research to identify the best methods as well as the language about cost effectiveness would address Dr. Matern's concerns. Dr. Matern replied affirmatively as long as the recommendation specifically addresses cost.

Dr. Chen asked whether it would be possible to include an exception in the Common Rule that would allow the use of NBS DBS for research. Dr. Bocchini anticipated that the changes in the Common Rule would be articulated across the spectrum of research done with residual clinical samples. NBS would be one domain of that broader set. It is unlikely that the NPRM would include changes specific to NBS.

Dr. Melissa Parisi expressed her concern that the wording of the recommendations indicates parties (the HHS Secretary and the states) that are a little different than those that will actually be involved in developing standards and guidance for IRBs, including OHRP. She was also concerned that the development of new methods mentioned in Recommendation 3 could be considered research. The term "new methods" is ambiguous. New methods for new conditions might be considered research while new methods that are variations on current screening approaches might not. She was also concerned about the amendment offered by Dr. Botkin, specifically that it might be a bit prescriptive for the Secretary, and about its implications for those engaged in supporting NBS-related research with federal funding.

Dr. Bocchini asked for suggestions for revising Dr. Botkin's amendment to make it more appropriate for NICHD and the other organizations that would be involved. Dr. Parisi indicated that her group would work on revising it. Dr. Bocchini also agreed that the recommendations should also include the various stakeholders with which the Secretary should consult, not just the states.

VOTE: Dr. Bocchini indicated that the suggestions offered by Committee members and organizational representatives would be incorporated into Recommendations 2-5. He then asked the Committee to vote to approve Recommendations 2-5 as amended. None of the Committee members recused themselves from the vote. All 12 of the Committee members present voted to approve the recommendations.

Dr. Bocchini adjourned the meeting for the day.

VI. Committee Business: May 12, 2015

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

Dr. Bocchini welcomed the Committee members, organizational representatives, and other participants to the second day of the meeting and took the roll. Ms. Sarkar served as the DFO.

Voting members present were:

- Dr. Don Bailey
- Dr. Bocchini
- Dr. Jeffrey Botkin
- Dr. Fred Lorey
- Dr. Dietrich Matern
- Dr. Stephen McDonough
- Dr. Alexis Thompson
- Ms. Andrea Williams

Ex Officio Members present were:

- Agency for Healthcare Research and Quality: Dr. Denise Dougherty,
- Centers for Centers for Disease Control and Prevention: Dr. Coleen Boyle
- Food and Drug Administration: Dr. Kellie Kelm
- Health Resources and Services Administration: Ms. Joan Scott
- National Institutes of Health: Dr. Alan Guttmacher

Organizational representatives participating in the meeting were:

- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State and Territorial Health Officials (ASTHO): Dr. Christopher Kus
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes: Dr. Siobhan Dolan
- National Society of Genetic Counselors: Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

VII. Long-Term Follow-Up in Newborn Screening: An Update on AGMG's Work on the NBSTRN and NCC Laboratory Procedures and Standards Subcommittee Update –Timely Newborn Screening Project and Other Projects

Amy Brower, Ph.D.
Project Manager
NBSTRN/NCC
American College of Medical Genetics and Genomics
Bethesda, MD

Dr. Amy Brower updated the Committee members on the work being conducted by ACMG in the area of LTFU up of individuals diagnosed as a result of NBS. These efforts are coordinated through the NBSTRN and the National Coordinating Center for the Regional Genetic Services Collaboratives (NCC).

Background
NBS is a series of interconnected activities that begins before birth. Each of the babies born in the United States receives screening for more than 50 conditions. Newborns who screen positive undergo a series of confirmatory tests. Screening and short-term follow-up take place with a state-based public health system; diagnosis, treatment, and management takes place in pediatric care centers. The handoffs from prenatal care to public health to clinical care provides an opportunity to capture longitudinal health information for infants diagnosed by NBS. The NBS system is intended to be comprehensive (from screening through LTFU through a medical home). All conditions identified through NBS are chronic and require medical services throughout an individual's lifetime. There is no national system for collecting and analyzing this information.

The Newborn Screening Saves Lives Reauthorization Act of 2014 includes two directives concerning LTFU. Section 3 extends a grant program to evaluate health outcomes of individuals with heritable disorders through adolescence. Section 9 authorizes the HHS Secretary to expand the Hunter Kelly Newborn Screening Research Program to provide research and data for newborn conditions under review by the ACHDNC and to conduct pilot studies on conditions recommended by the Committee. Both of these activities include LTFU of diagnosed newborns. The law also extends the authorization of the ACHDNC for five years and gives the HHS Secretary the option of continuing it beyond that time.

The ACHDNC defined the key features of LTFU in 2008 and provided further guidance in 2011 by identifying the overarching questions it should answer. The Committee's statement on LTFU called for timely and effective communication and information-sharing among patients and families, clinicians, laboratories, public health agencies, researchers, and community support services. Key features of LTFU include the assurance and provision of quality chronic care management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan. The four major components of LTFU are care coordination through a medical home, evidence-based treatment, continuous quality improvement, and new knowledge discovery. The questions follow the four components of LTFU and are framed from the perspective of the state and nation, primary and specialty health care providers, and the affected families. The questions should be used to guide the development of LTFU data systems, quality health indicators, and specific data elements for evaluating the NBS system.

ACMG Coordinating Centers

ACMG operates two coordinating centers that include LTFU efforts. NBSTRN was established in 2009 as part of the Hunter Kelly Newborn Screening program and works to improve the health outcomes of newborns by creating infrastructure and resources to support research in NBS. ACMG operates NBSTRN through a contract with NICHD. The second center, the NCC is funded by HRSA and works to strengthen and support the genetics and NBS capacity of the states for patients and families across the lifespan. Dr. Watson is the principal investigator for both coordinating centers.

LTFU efforts at NBSTRN and NCC take into consideration several aspects unique to NBS. Stakeholders represent diverse entities and concerns ranging from state NBS programs to clinicians to affected individuals and their families. Data collection efforts require working with more than 50 independent entities (state departments of health) and extend to a variety of care settings. NBSTRN and NCC efforts focus on creating tools to support longitudinal data collection activities by researchers and public health teams.

The development of LTFU tools and resources is coordinated through three groups within ACMG: the Joint Committee, NBSTRN, and NCC. The Joint Committee was formed by NBSTRN and NCC. It consists of experts working to define the common data elements (CDEs) that form the basis for longitudinal clinical data collection. The focus of this effort is the conditions that make up the RUSP. The Joint Committee includes 14 subject matter experts from the NCC LTFU Data Workgroup and 22 members of the NBSTRN Clinical Centers Workgroup, as well as representatives from National Library of Medicine, the CDC, and the NIH Office of Rare Disease Research (ORDR). The CDEs developed by the group form the basis of an information system of standardized datasets, case report forms, secure data collection, and sharing and data management tools. The datasets are key to understanding the effects of NBS and contribute to the understanding of the natural history of the conditions. They also help researchers identify inequalities in health care delivery and facilitate quality improvement. The longitudinal datasets can be used for clinical and translational research, to establish best practices, to advance the understanding of conditions, to assess the effect of screening for new conditions, and to assess the effect of novel treatments on outcomes.

The Joint Committee's efforts to create CDEs focused on the 32 core and 26 secondary RUSP conditions and on new conditions under consideration by the ACHDNC. The efforts also considered the four LTFU components identified by the Committee and the directives of the Newborn Screening Saves Lives Act. CDEs were formulated first through a development phase and then through a consensus phase. NBSTRN grantees incorporated the CDEs into their research efforts.

The CDEs form the basis of efforts within NBSTRN to create an informatics infrastructure available to NBS researchers. NBSTRN is charged with facilitating NBS research through the development, maintenance, administration, and enhancement of resources to support investigators focused on new technologies, new conditions, and treatment and management approaches. Tools and resources provided by NBSTRN facilitate research by supporting analytical validation, clinical validation, and clinical utility to help translate discoveries to public health and clinical care.

One of these tools, The Longitudinal Pediatric Data Resource (LPDR), is a secure informatics systems for the collection, sharing, management, and analysis of conditions identified through NBS as well as conditions that might benefit from NBS. The LPDR includes the Joint Committee's CDEs and the NBSTRN disease-specific data elements, which are organized into clinical case reports built into a secure informatics system that facilitates data analysis. The tool also provides resources for planning research, collecting and contributing data, querying data, and reporting and sharing LTFU data. Users can search CDEs by condition, clinical time point, or keyword and organize and upload the results in a single step. The LPDR includes CDEs for conditions across the spectrum of NBS. Forty-six conditions have consensus CDEs, while others are in the draft stage, in development, or in the queue for future efforts. The number of CDEs in use vary across conditions, researchers, and condition categories and are organized into clinical case report forms by clinical workflow. The clinical case report forms are organized into a Research Electronic Data Capture database that facilitates standardized, longitudinal data collection across the lifespan. The LPDR provides a secure infrastructure to support the collection and aggregation of consented clinical information. Level 1 of the infrastructure was designed to train researchers in the use of the LPDR

and Level 2 was designed for active LTFU follow-up projects. Currently, the LPDR is being used to study the natural history of currently screened NBS conditions and for pilot studies of candidate conditions and novel technologies.

The NCC's efforts are focused on LTFU in public health and seeks to leverage the seven Regional Genetics Services Collaboratives. State NBS programs collect information on all of the more than 4 million babies born each year. Having a single point of information capture represents the ideal implementation of LTFU efforts. Using the Joint Committee and NBSTRN's CDEs to collect information may make a nationwide public health dataset possible.

The NCC works to coordinate and accelerate LTFU throughout the Regional Collaboratives. Using the CDEs, the NCC LTFU Data Workgroup developed a set of 14 overarching questions that are now being used in pilot studies within the Regional Collaboratives. The questions represent aggregate information and can be answered using the case-level data in the LDPR.

Case Studies
Dr. Brower highlighted two case studies that illustrate the use of the CDEs and LPRD in LTFU.

SCID is characterized by the lack of a functioning immune system, is fatal in the first two years of life without treatment, and usually occurs in newborns without a family history of the disease. Because it is not readily apparent at birth and because early diagnosis is essential for lifesaving treatment, the condition has been recognized as a candidate for NBS since 2005. Several SCID pilot studies were performed beginning in 2008. It was added to the RUSP in May 2010.

The goal of the National SCID Pilot Study was to provide comprehensive NBS for SCID for as many newborns as possible (currently 70 percent of newborns are screened). The NBSTRN Coordinating Center serves as the administrative core for the project, which utilizes several NBSTRN tools. The project used several uniform and SCID-specific CDEs to support the collection of LTFU, specifically the diagnosis of SCID and T-cell-related lymphocyte deficiencies. In 2014, the study reported on 11 SCID screening programs and established a population-based incidence for SCID and other conditions with T-cell lymphopenia. It also documented health outcomes by treatment type. The work was made possible by the use of shared data elements and the central collection tool created by the NBSTRN.

A second case study highlighted the use of genomics in the newborn period. In 2010, NICHD the National Human Genome Research Institute, and ORDR sponsored a workshop to identify elements of trans-NIH research that would lead to the application of new genomics concepts and technologies to NBS and child health. The workshop was the genesis of the NIH's Newborn Screening, Sequencing and Genomic Medicine Public Health Program (NSIGHT), which consists of four pilot projects that explore the implications, challenges, and opportunities associated with the possible use of genomic sequence information in the newborn period. Goals related to collecting CDEs for the pilot studies included fostering research in the areas of gene discovery, phenotypic spectrum of rare variants, modification of genes for metabolic conditions, and pharmacogenomics studies. The four research groups were encouraged to share research with each other and across the NBSTRN network.

Although the four studies use different study designs, they share some of the same populations. Dr. Brower anticipated that the projects would develop CDEs that are specific to the research populations, including the neonatal intensive care and health children cohorts. The NSIGHT project hopes to use the CDEs to foster sharing of accumulated data within the LPDR, among the NSIGHT teams, and within each NSIGHT team. These efforts will provide a foundation for future follow-up of newborns consented into these studies.

Committee Discussion:

- In response to a question concerning the possibility of the Committee's LTFU Subcommittee working more closely with ACMG, Dr. Bocchini indicated that the new workgroups were designed to address the issues that must be addressed for the Committee to move its work

forward; however the various subcommittees will continue to exist. The LTFU Subcommittee will need to work more closely with organizations such as ACMG.

- An organizational representative who formerly served as a subcommittee chair noted that the Committee and its subcommittees could provide guidance, but would not be able to do the work being done by ACMG.
- Dr. Brower responded to a question concerning ways to encourage clinicians to enter data into the LPDR by stating that the studies use different strategies. In some cases, the clinicians are the funded researchers. Another way is to pay for the resources for entering data and to make the uploading of the data as easy as possible. NBSTRN created definitions and annotations to enable data abstractors and others who enter data to better understand what they are entering. NBSTRN also plans to conduct a retrospective look at what did and did not work and incorporate successful strategies in future efforts.
- A participant noted that long-term sustainability of the data collection is an issue that needs to be considered, especially when registries are being set up and as follow-up data is being collected. Additionally, there are registries that consist of patient-entered data for a couple of conditions on the RUSP. These should also be considered as possible LTFU resources.

VIII. Public Comments

Ms. Elisa Seeger, President, Aidan Jack Seeger Foundation: Ms. Seeger, who lost a son to adrenoleukodystrophy (ALD) due to late diagnosis, advocated for the addition of the condition to the RUSP. NBS allows families with a child with ALD to monitor and treat their children prior to the onset of symptoms. She responded to several concerns about ALD screening raised during the previous Committee meeting by stressing that the risks of problems related to sedation of infants for MRI are far outweighed by the benefits of MRI in children suspected of ALD based on NBS, by noting that bone narrow transplants would only be performed in cases where monitoring results indicate that ALD has been triggered, and by pointing out the benefits of monitoring and treatment for boys with adrenal insufficiency.

Janice Sherwood, Founder, Fight ALD: Ms. Sherwood described the diagnostic odyssey that preceded her son's late diagnosis with ALD and his death six months later. This experience led her to start Fight ALD, which is focused on educating providers and medical students. In 2014, Fight ALD helped introduce and get passed a bill to implement ALD NBS in California; however, the bill requires that ALD screening be added to the RUSP prior to implementation in the state. She urged the Committee to recommend the addition of ALD to the RUSP. She also reported on legislative efforts to implement screening in multiple states.

Jean Kelley, Stop ALD Foundation: Ms. Kelley described how her son's condition has declined over the past 20 years since he was diagnosed with ALD at age 6. She responded to the Committee's concerns about the sedation of infants and toddlers required for serial MRIs and bone narrow transplants by stating that parents would choose to sedate children long enough to gain the information provided by MRI. Parents also view bone marrow transplants and gene therapy as lifesaving options. NBS for ALD provides an opportunity for families to obtain early intervention and for their children to have a healthy and fulfilling life.

Dr. Bocchini stated that the Committee planned to have the ALD evidence review completed for a vote during the August meeting.

Mr. Dean Suhr, MLD Foundation: Mr. Suhr stated that the MLD Foundation has long been interested in the requirement for a disease-altering, viable therapy as one of the factors leading to the addition of a condition to the RUSP. The MLD Foundation will host a RUSP roundtable on August 26 in Rockville, MD, in conjunction with other advocacy organizations, medical professionals, policy makers, regulatory officials, and payers. The meeting will focus on the origin of the viable treatment requirement and how it affects NBS and public health. Participants will also discuss the potential effects of the use of genetic sequencing as a newborn screening tool.

IX. Update on ALD

Alex Kemper, M.D., M.P.H, M.S.
Condition Review Workgroup
Clinical Research Institute
Department of Pediatrics
Duke University

Dr. Alex Kemper updated the Committee on the status of the CRW's work on X-linked ALD. He anticipated presenting the group's final findings at the August Committee meeting.

X-linked ALD is a peroxisomal disorder that affects the adrenal cortex and the central nervous system. It has a broad phenotype that varies in onset and severity and primarily affects males. Of particular concern is the high proportion of affected individuals with the central nervous system manifestations who develop adrenal insufficiency.

The CRW conducted a thorough literature review. The review identified approximately 170 publications for inclusion in the final report.

The CRW focused on the forms of the condition that benefit in childhood from early detection (i.e., cerebral ALD and adrenal insufficiency/Addison's disease). Secondary targets include Zellweger's syndrome and other peroxisomal disorders; these would primarily benefit from early identification and treatment as a result of NBS.

The genetics of X-linked ALD are complex and it is difficult to predict phenotype. Screening tests are currently available and there is active research in this area. Diagnosis is based primarily on measurements of very long chain fatty acids (VLCFA) in plasma; the cerebral form can be diagnosed by MRI findings. The primary treatment for the cerebral form is hematopoietic stem cell transplantation; the adrenal form is treated with steroid replacement. There is a high degree of overlap between the childhood cerebral ALD forms and the likelihood of developing adrenal insufficiency.

With regard to pilot screening studies, Dr. Kemper indicated that there seems to be a low false positive rate. High throughput screening is possible. Currently, the false-negative rate is unknown.

There is much legislative activity around the country with regard to ALD. New York has been screening since December 30, 2013. New York uses a two-tier screening system. Tier 1 uses Tandem mass spectrometry (MS/MS); Tier 2 uses high performance liquid chromatography in addition to MS/MS. More than 300,000 newborns were screened in New York since December 30, 2013, with nine males being identified with the mutation. The Mayo Clinic has also been studying screening using anonymized DBS.

Dr. Kemper shared the algorithm used for third tier diagnosis and short-term follow-up. The ultimate diagnosis is based on elevated levels of VLCFA. The finding of ABCD1 mutations is supportive of diagnosing the specific form of ALD. Brain MRIs also help with the diagnosis of the cerebral form. Clinical evaluation can result in non-specific findings and symptoms can be common in the general public.

There are a few different strategies for the management of pre-symptomatic ALD. Generally, diagnosis is followed by referral to an endocrinologist due the high rate of adrenal insufficiency. The child is followed with MRIs; abnormal MRI scores would indicate the need for a transplant. Gene therapy is still considered experimental. A parallel cohort design study comparing matched individuals who received transplantation earlier in the disease course with those who had transplants later in the disease course, found that the five-year survival compared to historical controls was 66 percent.

Dr. Kemper reported that decision modeling for ALD is ongoing; the first Technical Expert Panel (TEP) call took place in April, and two more have been scheduled. The structure for the decision model is

complete and the parameters are being input from the evidence review. The results of the population-level modeling will be shared with the TEP prior to presenting the findings to the ACHDNC.

APHL will conduct the public health systems impact analysis for ALD by surveying the states to determine what they would require to implement ALD screening. APHL has prepared a factsheet on ALD screening and will field the survey shortly. On May 14, APHL will host a webinar with survey respondents to review the factsheet.

Committee Discussion:

- In response to a question concerning whether molecular genetic testing should be part of the screening process, Dr. Kemper indicated that a molecular result does not result in a final diagnosis, which relies on the measurement of the VLCFA and MRI findings. The only state that screens for ALD does a molecular diagnosis after a Tier 2 test is positive. Dr. Michele Caggana added that the DNA test does not need to be part of the screen. Her group does it as a courtesy to providers. It has detected mutations in the boys with ALD and in the carrier girls. Referrals are made based on the Tier 1/Tier 2 results and the extra sequence information at the time of referral.
- A Committee member was interested in learning how the transplant recipients mentioned by Dr. Kemper were doing eight years after the study. Dr. Kemper indicated that the CRW tries to follow up with researchers in this type of situation. The transplantation process has improved significantly since the study.
- A Committee member asked whether the CRW intends to include an evaluation of the harms associated with ALD screening. She also inquired whether babies could be categorized as to their ALD phenotype (particularly for cerebral ALD) given the various diagnostic mechanisms. Dr. Kemper indicated that the CRW is looking at both benefits and harms (harms are harder to classify). Because of the numerous mutations and the lack of genotype/phenotype correlation, it is not possible to predict age of onset; this is why there is a need to follow individuals over time using MRI. Individuals diagnosed with X-linked ALD need to be followed to determine whether they need transplantation or whether they develop adrenal insufficiency. Dr. Caggana added that baseline MRIs are generally taken around six months of age, and transplants are offered when MRIs begin to show changes. Dr. Kemper noted that the level of the VLCFA is not predictive.
- In response to a question concerning whether the cases of Zellweger's disease identified through ALD screening would be counted as false positives, Dr. Kemper indicated that the CRW is cataloguing the number of peroxisomal storage disorders. For the purposes of the data, the group is looking at the primary targets (i.e., the other forms of X-linked ALD).
- A Committee member indicated that it would be helpful for the Committee to define what constitutes false positives and false negatives for ALD.
- A meeting participant observed that the other targets (such as Zellweger's) that are related to ALD could prove to be valuable in understanding their diagnosis.
- In response to a question about the ALD screening program in the Netherlands, Dr. Kemper indicated that the CRW had done some initial work on this project and could review the updated findings.
- Dr. Kemper confirmed that information on the ALD screening test based on the New York experience would be available in August. It is unlikely that the CRW will have data on missed cases of ALD. It would be difficult to determine the sensitivity or specificity of the test.
- An organizational representative noted that there is a new MRI technology that uses a larger magnet and is faster than those currently in use for most cases of children picked up by NBS. This machine might make it possible to run scans without sedation in approximately 15 minutes. She also cautioned against describing MRIs as predicting whether someone will develop cerebral ALD; MRIs show the actual presence of white matter disease.

X. Adjournment

Dr. Bocchini thanked all of the attendees for their participation in the meeting. He reiterated that the subcommittee structure of the ACHDNC will remain the same. Work is ongoing to re-orient them to the

new activities of the Committee. As a result of the reauthorization, the Committee will add two new workgroups; these new groups met on May 11 to begin work on their charges, membership, and activities. The first new workgroup will focus on timeliness and will be co-chaired by Dr. Kelm and Ms. Wicklund. The second workgroup will be chaired by Dr. Kemper and will focus on cost analysis. Additionally, Dr. Botkin chairs the Pilot Study Workgroup; this group has already started working on its charge.

The next meeting of the ACHDNC will take place on August 27-28, 2015.

With no additional business to address, Dr. Bocchini adjourned the meeting at 11:50 a.m.