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

Summary of 5th Meeting
September 11-12, 2014

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) was convened for its 5th meeting at 9:30 a.m. EDT on Thursday, September 11, 2014. The meeting was adjourned at 2:21 p.m. EDT on Friday, September 12, 2014. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

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I. Administrative Business: September 11, 2014

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 fifth meeting of the Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC). Ms. Debi Sarkar, the Health Resources and Services Administration's (HRSA) Designated Federal Official (DFO), also greeted the participants and reviewed the rules concerning lobbying for Committee members.

Dr. Bocchini took the roll for the first day of the meeting. Voting members present were: Dr. Bocchini, Dr. Don Bailey, Dr. Jeffrey Botkin, Dr. Charles Homer, Dr. Fred Lorey, Dr. Dietrich Matern, Dr. Stephen McDonough, Ms. Catherine Wicklund, Dr. Alexis Thompson, Ms. Andrea Williams.

Ex-offico members present were:

- Agency for Healthcare Research and Quality: Dr. Denise Dougherty
- Centers for Disease Control and Prevention: Dr. Coleen Boyle
- Food and Drug Administration: Dr. Kellie Kelm
- Health Resources and Services Administration: Dr. Michael Lu
- National Institutes of Health: Dr. Melissa Parisi

The Designated Federal Official, Ms. Debi Sarkar was present.

Nonvoting organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Frederick Chen
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- American College of Obstetricians and Gynecologists (ACOG): Dr. Nancy Rose
- Association of Maternal and Child Health (AMCHP): Dr. Debbie Badawi
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes (MOD): Dr. Siobhan Dolan
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

B. Approval of May 2014 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 a copy of the minutes for the May 2014 DACHDNC meeting was provided in the briefing book for this meeting. The Committee members in attendance unanimously approved the minutes.

II. Pilot Study Work Group Update

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

Dr. Botkin updated the Committee on the goals, tasks, and planned activities of the Pilot Study Work Group. The group focuses on supporting current pilot studies and evaluation efforts. It is also responsible for identifying resources that could support pilot studies and evaluation, providing recommendations to the Secretary of Health and Human Services (HHS) in support of the DACHDNC condition nomination process, studying approaches to developing a network of states that could support the infrastructure needed to conduct pilot studies, and identifying information required to move a nominated condition to the evidence review process. The group will meet by conference call in October and anticipates conducting a panel presentation on relevant pilot studies during the next DACHDNC meeting.

III. The Inborn Errors of Metabolism Collaborative – Update

Susan Berry, M.D.
Professor and Director
Division of Genetics and Metabolism
Department of Pediatrics and Genetics, Cell Biology, and Development
University of Minnesota
Minneapolis, MN

Dr. Susan Berry reported on the history and current activities of the Inborn Errors of Metabolism Collaborative (IBEMC), which is working on a long-term follow-up (LTFU) and treatment protocol. This effort began in the Region 4 Genetics Collaborative, with the review of treatment plans contributed by partners, identification of essential elements of LTFU, and initiation of data collection plans. The project evolved into an effort to develop a larger scale, web-based follow-up record, the Inborn Errors of Metabolism – Information System (IBEM-IS), as a platform for research that could serve as a model for a national platform.

The IBEC-IS initially focused on medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Initial steps included developing a demographic database and condition-specific data elements with the goal of developing data that was as uniform as possible. The project also defined issues for short-term follow-up and LTFU, developed processes for adding additional disorders, and developed processes for documenting consent to allow continuing contact and to engage subjects as participants in future research trials.

The IBEM-IS was initially funded in 2004 by HRSA through the Region 4 LTFU Work Group. Data entry into the IBEM-IS for MCAD began in 2007. Funding for the project continued from 2007 through 2011 through the HRSA-funded Region 4 Priority 2 Project LTFU. During this time, additional regional genetics collaboratives, including Heartland and the New York-Mid-Atlantic Consortium, joined the effort. Since

2011, the project has been partially funded through the National Institutes of Health Inborn Errors of Metabolism Collaborative (IBEMC). Beginning in 2013, the IBEM-IS included all inborn errors of metabolism (IEMs) listed on the Recommended Uniform Screening Panel (RUSP).

The Newborn Screening Translational Research Network (NBSTRN) is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) through a contract with ACMG. It maintains, administers, and enhances resources to support projects related to newborn screening (NBS), particularly with regard to new technologies, new conditions, and new treatment and management approaches. NBSTRN has several research tools, including the Virtual Repository of Dried Blood Spots, the Longitudinal Pediatric Data Resource (LPDR), and the Region 4 Stork (R4S) tool. Most of the work described by Dr. Berry related to the LPDR. Additionally, the project benefitted from a high level of cooperation with the Joint Committee of the National Coordinating Center's LTFU Committee.

The goals of the collaboration between IBEMC and NBSTRN-LPDR are to improve knowledge about the clinical history of persons with IEMs on a long-term basis and to gather evidence about effective management and treatment strategies for those with IEMs. Methods employed as part of the project include elements from treatment protocols, other data sets, and literature reviews; prospective informed consent; and data gathered using web-based, password-protected data entry forms on the Research Electronic Data Capture (REDCap) system.

The IBEMC collects data on all of the primary core conditions on the RUSP as well as secondary conditions. As of January 2014, the system included approximately 1,500 records, with phenylketonuria (PKU) and MCAD having the highest number of records. As of August 2014, the system contained records for almost 1,700 individuals aged less than one to 62 years of age, with 289 of those being over age 18. There are slightly more males than females in the system. The majority of the records are for White/Europeans, with significantly smaller numbers of African Americans/Black, Hispanic/Latino, and other racial groups represented. Eighty-two percent of the participants were diagnosed by NBS, and 18 percent were diagnosed by family members, clinical diagnosis, or laboratory abnormality. Overwhelmingly, people receive genetic counseling (90 percent). Of the 771 for whom data was available on days from birth to intervention, the average for all disorders was 20.5 days. The average for critical disorders was 12.4 days and for non-critical disorders was 30 days. Approximately 80 percent of those in the system agreed to be re-contacted in the future for research purposes.

Dr. Berry reported on the findings of a study on early complications of MCAD deficiency concerning the impact of the C8 value and of the genotype on early complications. The study population included 202 subjects diagnosed by NBS and 17 by clinical presentation out of a total population of 247. The study found that higher C8 values identified by NBS are more likely to be associated with laboratory abnormality, symptoms, and homozygosity for the common allele and those infants with higher C8 values are more likely to have clinically concerning symptoms or lab values. The IBEMC recommend extra precautions in assessments for infants with higher C8 values on NBS.

Currently, the IBEMC is analyzing the collected data through condition-specific research programs. Additionally, the project continues to enroll participants, collect data, add new participating centers (there are currently 27), collaborate with other research projects, and add specific research surveys. The project also hopes to help public health leaders make informed decisions about NBS investments. Dr. Berry anticipates that six to eight papers will be published based on the initial data sets. More information on IBEMC is available at www.ibem-is.org.

Committee Discussion:

- In response to a comment about the 12-day average to intervention, Dr. Berry explained that the average was affected by two major outliers in the data; the average is closer to five days. There are some disorders that precipitate prior to the time that they can be captured by NBS.
- Dr. Berry clarified that children who are enrolled in the project have data collected with each subspecialist visit. Each visit produces a small summary of the visit. This will provide granular information over time. There are also opportunities for collecting data from parents, although the emphasis would be different but complementary.

- Concerning the ability to generalize the system beyond the convenience sample and disparities in care, Dr. Berry indicated that there is an effort to develop a subset of approximately 35 NBS-linked data elements that could be collected in a more population-based way and that could be used to develop an LTFU snapshot. The goal would be to provide a more uniform and succinct data set for the denominator.
- The data sets for the lysosomal disorder data sets should be able to be consolidated, but the issue is mapping the data sets. It is unclear whether the pharmaceutical companies are willing to do this. A subcommittee member reported that work on the lysosomal storage disorders (LSDs) data sets is almost complete and should be running about the same time NICHD awards the contract for the Pompe pilot.
- With regard to the parent/caregiver perspective, a Committee member noted that this group could get lost in the system. There is a need for more research on parents and caregivers. Dr. Berry stated that the data set includes elements on special needs, special education, referral to services, and distance to providers, which is collected during the visit with the clinicians.
- In response to an inquiry about the way that the IBEMC-IS and the LPDR work together; Dr. Berry indicated that the work with LPDR was the starting point from which the data set was built. She explained how the REDCap data sets were developed and the way that the IBEMC tools were designed for use with the LPDR.
- A Committee member expressed concern over the very low number of racial minorities in the data set and the possibility of bias in the recruitment process. Another Committee member noted that the data set does not include individuals with hemoglobinopathies. Dr. Berry responded that she did not believe that there was any potential bias in the way patients are identified for recruitment. The clinic staff is responsible for talking to patients about participating, which could possibly be a point at which bias could creep in. PKU and MCAD, which represent the largest groups of patients in the data set, are Caucasian disorders; as a result, some of the bias comes with the disorders.

IV. The Impact, Products, and Future Applications of the Region 4 Stork Collaborative Project

Piero Rinaldo, M.D., Ph.D.
Division of Laboratory Genetics
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Dr. Piero Rinaldo discussed the origin and evolution of the R4S project, the impact of the R4S productivity and post-analytical interpretive tools, and the applicability of the project beyond tandem mass spectrometry (MS/MS).

The R4S began as a regional laboratory quality improvement project involving all seven states in Region 4. It received two cycles of funding from HRSA (2004-2012) before funding transitioned to NICHD. Currently the project includes 235 programs in 66 countries, including almost full participation from states in the United States. There are approximately 1,130 active users. R4S collects data in the form of laboratory results (more than 1.2 million data points from approximately 18,000 patients). The R4S website has received almost 900,000 page views. The post-analytical interpretive tolls have been utilized 90 million times, with each day averaging 100,000 uses. Productivity tools provide a way to evaluate evidence of any condition and to compare different conditions. Dr. Rinaldo stressed that the R4S collaborative project has made worldwide collaboration possible, citing the 247 co-authors of the project's first published article.

The peer comparison tools allow sites to see, in a confidential manner, how their reference percentiles and cut-off values compare to all others in the project. R4S can generate these plots for every condition. The project has also worked to determine abnormal/normal/cumulative percentiles and cut off values by combining all of the data. The project is revisiting the definition of an abnormal result (traditionally defined

as being above or below a certain value). Within the project, the definition of normal is based on when the disease range begins to be seen.

The R4S has moved away from static, clinical evaluation to a process that is constantly evolving. On average the project adds five true positive cases per day. The system allows users to incorporate differences in the recognition of conditions and in the differential diagnosis between multiple conditions with similar phenotypes. The project also shows how ratios that are more likely to avoid false negatives are being used.

Dr. Rinaldo discussed the impact of R4S on algorithms used in NBS. Instead of a single, sequential algorithm, R4S uses a parallel algorithm that evaluates all factors simultaneously in a post-analytical tool that produces a single score. The algorithms also help with differential diagnoses by covering primary conditions and secondary targets.

The main products of the R4S project are the post-analytical tools. These help provide clinically useful answers to questions for which the answers are: yes or no (for a particular condition), one or the other (differential diagnosis between two conditions), and one out of a group (many conditions).

During the period during which the R4S system has been in use at the Mayo Clinic, the detection rate has been fairly stable, but the false positive rate has dropped to 0.024 percent, with a positive predictive value of 70 percent. The average false positive rate in 28 programs is 0.51 percent. The R4S used this information to develop a more practical measure, the false positives per week measure.

Dr. Rinaldo also discussed the applicability of R4S beyond MS/MS. The RUSP currently includes 57 primary and secondary conditions, but factoring in the addition of other conditions that have been, are, or could soon be under consideration plus the lysosomal conditions, the total possible number of NBS tests could exceed 100. Multiplexing could be an option for handling a significantly expanded list of tests. Other factors that need to be considered are analytical robustness and reproducibility, in-depth clinical validation, and performance metrics that greatly exceed historical standards. Dr. Rinaldo stated he believes that more conditions should be added to the RUSP, but stressed that there must be a reduction in the rate of false positives. His opinion is that the goal should be fewer than 100 false positives per day combined for all tests. Reducing the number of false positives will reduce recalls and repeat analyses, disruption of care, emergency room visits and hospital admissions, confirmatory testing, referrals to multiple specialists and second opinions, and effects on families.

With regard to improving performance, Dr. Rinaldo recommended making better use of existing approaches. He reported on a study that compared the results of NBS (based on cut-off values) to what would have happened using the R4S tools in California over a six-month period. The study found that using the R4S tools would have reduced the false positive rate from 0.26 percent to 0.09 percent; if all of the other possibilities were adopted, the false positive rate would have been reduced to 0.02 percent. This would dramatically reduce the number of false positives nationwide and create more room for new conditions.

Committee Discussion:

- Dr. Rinaldo responded to a question, about why states that are participating in the R4S project do not currently have the lower false negative rate, by indicating that many of the states are using the tools, however, he was unaware of the performance metrics being used. Other independent reports indicate improvements after states begin using the tools. He anticipated hearing results from Georgia at the upcoming APHL meeting.
- Concerning the relationship between the R4S efforts and the Centers for Disease Control and Prevention's (CDC) proficiency testing effort, Dr. Rinaldo indicated that proficiency testing is a point-in-time measurement of accuracy and precision. The R4S project is focused on providing tools for everyday work.

V. Public Comments

Sarah Wilkerson, Board Member, Save Babies through Screening Foundation: Ms. Wilkerson, who stated she lost a son to undiagnosed MCAD, thanked the Committee for its efforts to research NBS timeliness issues. She asked whether the Committee had any updates on the plan to work with the Joint Commission to add timeliness guidelines and what steps could be taken to ensure that laboratories follow the same guidelines for turning around test results. Additionally, she recommended that the CDC or APHL take over the database developed by the *Milwaukee Journal Sentinel* that tracks performance metrics for timeliness of hospitals, which would help identify states and hospitals that need more follow-up and training to meet basic guidelines. States and hospitals should be encouraged to stick with the best practice guidelines created by the Committee. Ms. Wilkerson concluded by sharing a recent example of a child who had to wait eight days for positive test results for a carnitine uptake deficiency; she stated that it appeared that batching at the hospital level was the cause for the delayed test results.

Ms. Ann Moser, Kennedy Krieger Institute: Ms. Moser reviewed the currently available treatments for adrenoleukodystrophy (ALD) and reported on ALD screening pilot projects at the Mayo Clinic and the New York State NBS laboratory. She also described the follow-up network currently in use in New York State. Ms. Moser advocated for the inclusion of ALD on the RUSP on behalf of the ALD community.

Mr. Steve Barsh, Founder, The Stop ALD Foundation: Mr. Barsh expressed gratitude on behalf of The Stop ALD Foundation for the Committee's decision to move ALD to the external expert review phase, but also expressed disappointment that the review has still not begun eight months after that decision. He urged the Committee to implement more specific review timelines, given the existence of an ALD NBS test and a follow-up process that works. He stated that ALD screening will save lives and reduce the costs of caring for children diagnosed with the condition compared those who go undiagnosed.

Ms. Elisa Seeger, President, Aidan Jack Seeger Foundation: Ms. Seeger, who stated she lost a son to ALD, reviewed the success of New York state in identifying six boys and two girls with ALD by NBS with no false positives since NY began testing all newborns for ALD in late December 2013. She advocated for the addition of ALD to the RUSP and stressed the importance of early diagnosis and treatment for ALD and the associated adrenal insufficiency.

Ms. Annie Kennedy, Senior Vice President for Legislation and Public Policy, Parent Project Muscular Dystrophy: Ms. Kennedy reviewed the incidence of Duchenne muscular dystrophy, which is the most common fatal genetic disorder diagnosed in childhood. She described efforts to develop an NBS test for Duchenne, the Duchenne NBS screening pilot project in Ohio, and further efforts to refine and streamline the analysis. She also described promising therapies under development in Europe and the cautious optimism that they could be approved for use in the United States. Ms. Kennedy indicated that her organization is ready to apply its national infrastructure to move Duchenne NBS initiatives forward in partnership with the Committee.

VI. Condition Review Update – Mucopolysaccharidosis I (MPS-1)

Alex Kemper. M.D., M.P.H., M.S.
Condition Review Workgroup
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Durham, NC

Dr. Bocchini stated that during its previous meeting, the Committee had agreed to begin considering a process for taking a condition off of the RUSP. After careful consideration, he decided that it was more important for the Committee to first complete outstanding activities related to strengthening the public

health impact assessment and completing the review of the two nominated conditions currently under consideration - MPS-1and ALD.

Dr. Alex Kemper began by describing MPS I as an autosomal recessive LSD caused by a deficiency of α-L-iduronidase (IDUA) enzyme. MPS-1 is a progressive, multisystem disorder with variability of clinical symptoms and a continuum of disease severity. The estimated prevalence is one in 100,000; the population-based screening studies indicate that the prevalence is higher (three to six in 100,000). MPS I represents two or three heterogeneous and overlapping syndromes. He described the characteristics of the severe form (Hurler syndrome), in which death occurs in early childhood, and the two attenuated forms (Hurler/Scheie and Scheie syndromes), which have a later onset and in which death occurs either in the teens or twenties or later in life. The severe form is the predominant form of the disease (75 to 80 percent of patients).

Screening for MPS I is based on IDUA enzyme activity detected in dried blood spots (DBS). Tests can be run using MS/MS or fluorometry. Diagnosis is based on IDUA enzyme activity of less than one percent; however, enzyme activity alone does not predict the phenotype. Increased glycosaminoglycan levels in urine are supportive of the diagnosis. Genotyping can be helpful if it reveals a known mutation, of which there are more than 100. The known IDUA-pseudodeficiency mutation is generally considered rare, although it might be more common in certain populations. Work on the genotype-phenotype correlation is ongoing.

Treatment for MPS I consists of hematopoietic stem cell transplantation (HSCT), HSCT and enzyme replacement therapy (ERT), or ERT alone. HSCT is associated with increased survival, preserved development, and improved mobility in patients with the severe form when compared to historical controls. There is little evidence regarding the HSCT in asymptomatic infants; the Condition Review Workgroup (CRW) needs to go back to the states that have done pilot studies to determine whether there is any unpublished data concerning HSCT in this group. Early treatment seems to be better, but the optimal timing of treatment is unclear. ERT leads to improvements in outcomes for patients with the attenuated form (based on a randomized clinical research trial among adult patients); however the benefits of ERT with asymptomatic attenuated MPS I are unclear. Harms associated with treatment are the need for chronic infusions and the possibility of antibody development.

The literature review for MPS I initially identified 194 articles; another 91 reports are under review for inclusion.

Dr. Kemper reported that Missouri is conducting an MPS I NBS pilot study. The state is doing full-population screening, although the results are not being reported through the usual NBS channels. Since January 2013, the state has screened 117,000 newborns using the digital microfluidics method and identified 57 positive samples. Of those, one case was confirmed as MPS I, 24 were pseudodeficiencies (the state believes it can decrease the number of these cases by changing the specificity of the screening), three were carriers, 24 were false positives, four are pending, and one was lost to follow-up. The overall false positive rate is 0.04 percent, and the in-house repeat rate is 0.49 percent.

Dr. Kemper also reported on the Illinois MPS I NBS validation study. So far, 12,400 specimens have been screened with 20 being rescreened and seven reported as positive. Of the presumptively positive results, four had pseudodeficiency, one was a false positive, one was a carrier, and one is still pending.

Summarizing the findings concerning screening for MPS I, Dr. Kemper indicated that IDUA can be measured, the screening algorithm is still being refined to balance case detection and false positives, and the most significant challenges relate to predicting the form/severity of detected cases.

Several issues remain to be resolved by the CRW. These relate to subpopulations that are more likely to have pseudodeficiency; the ability to predict the severity or form of the condition; current knowledge about genotypes of unknown significance and the early identification of attenuated forms; the importance of earlier initiation of treatment for the severe form; issues related to treatment that addresses brain involvement; following up with programs that are currently screening for MPS I; and looking into the use of MPS I registry information and other unpublished data. Next steps for the CRW include updating and

finalizing the evidence review, working with the University of Michigan on modeling the population benefits of screening, assessing the public health system impact, and finalizing the condition review report.

Dr. Kemper reported that the CRW has begun working on X-linked ALD. The disease has an overall prevalence of one in 20,000 and has three types. He reviewed the characteristics of the childhood cerebral, adrenomyeloneuropathy, and Addison disease forms. The condition is related to mutations in the ABCD1 gene, which is responsible for producing a protein that transports long-chain fatty acids into peroxisomes. Because of the poor genotype-phenotype correlation, it is difficult to predict the course of the disease. Screening is conducted using DBS and diagnosis is made based on mutation analysis, measurement of long-chain fatty acids, and MRI findings. X-linked ALD is treated with HSCT, adrenal hormone replacement therapy, and N-acetyl-L-cysteine. The CRW will look at the net benefits of the early initiation of treatment of those individuals identified through screening.

Committee Discussion:

- It was noted that the R4S project looks for several other LSDs in addition to MPS I. By conducting a multivariate analysis, the program could reduce the in-house repeat rate. Adding the amino acid disorders would further reduce the rate.
- In response to an inquiry about the risks that an individual with the attenuated form might receive an unnecessary transplant. Dr. Kemper acknowledged that there is a risk; however, there are international consensus guidelines on the characteristics that indicate when an individual should be transplanted. Factors include a neurological exam and enzyme levels (children with the severe form have close to zero enzyme activity). He anticipated that the risk would be low.
- A Committee member stressed that children with the severe form are unlikely to be transplanted because, to the trained eye, they are obviously different from those with other forms (i.e.., physical exam and x-rays show differences before neurological symptoms are apparent), especially in light of a positive screening.
- There was some disagreement among the participants over the need for laboratory testing to confirm diagnosis. Pediatricians would not normally pick up MPS I, but, with a positive screening, it is possible to distinguish which children need a transplant.
- Regarding mortality rates among those receiving transplants for both MPS I and ALD, Dr. Kemper indicated that this information is built into the modeling of the population benefits of screening. There is little information on long-term mortality among these transplant patients. Dr. Kemper believed that any effects would be seen soon after transplantation. The healthier the patient is at time of transplant, the lower the mortality risk.

VII. Condition Review Update –Public Health Systems Impact Assessment

Alex Kemper. M.D., M.P.H., M.S.
Condition Review Workgroup
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Durham, NC

Dr. Kemper indicated that the CRW would appreciate the Committee members' advice on the how best to assess the public health system impact (PHSI) of adding a condition to the RUSP. After briefly reviewing the efforts to develop the PHSI since 2012, he identified feasibility and readiness as the two key elements in the decision-making process.

The main factors related to feasibility are: the availability of an established screening test; a clear approach to diagnostic confirmation; a treatment plan that is acceptable to clinicians, individuals, and families; and

the ability to establish LTFU plans. Much of this information can be identified through the evidence review process.

Readiness becomes an issue once a state decides to include a condition and funding is made available; specifically, readiness is a measure of how quickly a state could implement screening for the new condition and what factors would prevent or delay a state from doing so. Programs that are in the "ready" phase are defined as being able to implement within one year, those that are in the "developmental" readiness phase are defined as being able to implement within one to three years, and those that are "unprepared" are defined as being needing more than three years to implement screening.

The evidence review process allows the Committee to make decisions around net benefit and the certainty of the benefit. Once the benefit has been determined, the PHSI comes into play. The CRW uses the DACHDNC Decision Matrix to guide its assessment of net benefit, feasibility, and readiness. Dr. Bocchini pointed out that two Committee members serve on each specific condition review group and there is much interaction between the full Committee and the condition review group.

If there is developing evidence of harm or no net benefit, the condition review group could inform the Committee of this evidence, which would influence the Committee's decision to move forward with the review or to stop the process.

Factors considered during the PHSI, include the ability to screen, short-term and long-term follow-up, organization of the NBS program, data and information exchange systems, direct costs, opportunity costs, and leadership and motivation.

Key stakeholders that have a direct impact on the system and that need to be considered include NBS program directors, NBS laboratory directors, public health commissioners, state government officials, laboratory and clinical specialists, primary care providers, and payers.

The PHSI approach proposed by the CRW focuses on the aspects that drive the DACHDNC's decision making process. In general, the CRW focuses on condition-specific issues, whereas good information concerning the general operation of NBS programs is available through the APHL and regional collaboratives (RCs). While the CRW strives to gather information of a more general nature from all of the states, it will seek to obtain more detailed information from those states that already have experience with a particular screening. The group will also work to identify a single, key point of contact within each state that can facilitate obtaining responses from others within the state. Dr. Kemper indicated that employing a standard approach to PHSI assessment will improve efficiency and consistency, facilitate comparisons, and be responsive to Office of Management and Budget (OMB) requirements.

Dr. Kemper identified several general issues related to NBS data collection and sources, including processes for adding conditions to state panels, existing NBS infrastructure, laboratory and reporting systems, and short-term and long-term follow up requirements. Much of this information is available through the Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) and the RC's.

Condition-specific issues related to data elements will be available, in part, through the condition review findings (e.g., validated screening methods, laboratory follow-up, diagnostic confirmation methods, short-term and long-term follow up needs, and the need for treatment centers and clinical guidelines). Some of the condition-specific information will be obtained through surveys of states with experience with a particular condition and from in-depth key informant interviews.

In summary, the condition review process consists of three basic components: the systematic evidence review, the determination of the population benefit (decision analysis), and the PHSI. The target for completion of these three components is nine months.

Dr. Kemper broke the PHSI down into five steps:

1. Work with the RC's to identify states that are or are planning to screen for a condition and identify the most appropriate survey respondents.

2. Identify the survey respondents in each state.
3. Prepare education material (e.g., fact sheet and webinar) for respondents to ensure that they understand the condition and the benefits of screening and early intervention.
4. Conduct the survey. The survey should be simple, focused on information needed by the DACHDNC to make a decision, and reusable.
5. Conduct in-depth interviews with key NBS and public health leaders in states that currently implement the screening for the condition under consideration.

Dr. Kemper shared some of the PHSI survey questions that were designed to help the CRW identify barriers and facilitators to screening. The questions will also help states determine where they fall in terms of readiness.

Committee Discussion:

- With regard to the definition of "unprepared" (readiness), a question was raised whether the rating means that the Committee does not believe that a state would be able to implement the screening within three years. Severe Combined Immunodeficiency (SCID), which was approved in 2010 but for which only 20 states are testing, was cited as an example of a condition that in hindsight would not have scored high in terms of readiness. It was suggested that the Committee should consider recommending conditions for addition to the RUSP even if it would take several years to implement the screening. Dr. Kemper explained that, in terms of the decision matrix, readiness relates to the decision to screen and the availability of funding. Readinesses to implement the task and providing treatment have been lesser issues.
- A Committee member asked if recommendations would be based on whether states are able to implement a screening and have the funds to do so, rather than strictly on whether there is evidence that screening will result in healthier children. Dr. Kemper indicated that the assessment of readiness level is not about whether a screening is beneficial but about what states need to do to in order to implement screening. Dr. Bocchini stressed the importance of partnering with states and identifying barriers. He indicated that the Committee would likely vote to include conditions that have a clear benefit even if states were not ready to implement them.
- The CRW will talk to specialists responsible for treating children identified through NBS as part of the overall evidence review process. It was noted that OMB rules make it challenging to conduct general surveys of specialists.
- With regard to the most appropriate individuals to interview as part of a condition-specific PHSI, a Committee member suggested that state NBS advisory committee members would be able to address most of the issues.
- Finding the most appropriate individuals within each state for purposes of the survey will be challenging, especially the first time this approach is used; however, making states aware of the goals of the effort should help to engage them in the process.
- A concern was raised that if a state indicated that they are not ready to implement screening for a condition the Committee recommends, states input on the public health system impact would not be helpful. Dr. Bocchini indicated that the feedback would influence how a condition is rated. Conditions rated as "A" would be ones for which there is general agreement that there is benefit in screening and that screening can be done. Barriers to timely implementation could be identified; if these barriers cannot be addressed, the rating of the condition would be affected.
- A Committee member recounted the DACHDNC's early discussions concerning the rankings. Initially, it seemed that only those conditions ranked A1 or A2 would move forward, while A3 and A4 ratings would require further discussion by the Committee and would benefit from demonstration projects to determine whether the rankings could be increased. In retrospect, SCID would have been rated as A3 or A4 and would not have been approved. A concern was raised that this approach could inadvertently slow down screenings and adversely affects children's health. Dr. Bocchini explained that the initial delay in the SCID approval related to a lack of data. SCID was one of the approved conditions used by Dr. Kemper to test the matrix; his analysis found that the same decision would have been reached using it.
- A Committee member noted that there was nothing in the matrix or outlined approach that addressed the cost benefit analysis of approving a condition (e.g., savings in long-term care for

each dollar spent for screening, etc.). Dr. Kemper indicated that the cost benefit modeling would fall under the population benefit analysis. Dr. Kemper anticipated being able to do more modeling moving forward than was done in the past, although he cautioned that it would be very difficult to determine the lifetime benefit. He indicated that because of the many uncertainties and nuances in the analysis, the validity of the estimate would always be in question.

- A Committee member suggested separating the process into two parts. The first part would be determining readiness. The second part, which would consist of the PHSI assessment, would be initiated once a condition was determined to have a readiness level of A. This would encourage states to provide feedback and would provide the Committee an opportunity to address identified barriers in its recommendations.
- A Committee member recommended doing more work to identify the barriers to implementation at the state level, especially those that are applicable to multiple states.
- A Committee member pointed out that approaching the assessment as a two-step process would result in making the overall review and recommendation process longer. Dr. Bocchini explained that the Committee elected to conduct the processes at the same time to shorten the timeline and to provide states with opportunities to provide in-depth answers to the Committee's questions. Following the decision concerning the Pompe recommendation, the Committee realized that it needed a stronger analysis of the PHSI.
- It was noted that the Committee's recommendations, even for conditions that cannot be implemented quickly, helps those responsible for NBS within states advocate for the addition of conditions to their respective state panels.
- The Committee members discussed how the PHSI assessment could be used, including ways it could be used to advocate for changes that would reduce barriers.
- The importance of funding issues, including the disconnect between who pays for NBS and who benefits from it, was discussed. Funding issues must be resolved before screening can begin.

VIII. Committee Business: September 12, 2014

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.

Voting members present were: Dr. Bocchini, Dr. Don Bailey, Dr. Jeffrey Botkin, Dr. Charles Homer, Dr. Fred Lorey, Dr. Dietrich Matern, Dr. Stephen McDonough, Ms. Catherine Wicklund, Dr. Alexis Thompson, Ms. Andrea Williams(morning only).

Ex-offico members present were:

- Agency for Healthcare Research and Quality: Dr. Denise Dougherty
- Centers for Disease Control and Prevention: Dr. Coleen Boyle
- Food and Drug Administration: Dr. Kellie Kelm
- Health Resources and Services Administration: Dr. Michael Lu
- National Institutes of Health: Dr. Melissa Parisi

Nonvoting organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Frederick Chen
- American College of Medical Genetics (ACMG): Dr. Michael Watson (morning only)
- Association of Maternal and Child Health (AMCHP): Dr. Debbie Badawi

- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes (MOD): Dr. Siobhan Dolan
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

IX. Laboratory Procedures and Standards Subcommittee Update – Timely Newborn Screening Project and Other Projects

Kellie B. Kelm, Ph.D.
Subcommittee Co-Chair
Scientific Reviewer/Biologist
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Devices Evaluation and Safety
Food and Drug Administration
Silver Spring, MD

Susan M. Tanksley, Ph.D.
Subcommittee Co-Chair
Organizational Representative
Association of Public Health Laboratories
Austin, TX

Dr. Kelm and Dr. Tanksley reported on the work the Laboratory Standards and Procedures (LS&P) Subcommittee has been doing for the past year on timeliness of NBS.

The Subcommittee was tasked with reporting on best practices to alleviate gaps and eliminate barriers to timely NBS and assessing whether current goals for timely sample collection, transit, and testing are appropriate for the current NBS system.

In January 2014, the DACHDNC recommended timeframes related to NBS:

1. Initial NBS specimens should be collected at 24 to 48 hours of life.
2. NBS specimens should be received at the laboratory within 24 hours of collection.
3. NBS results for time-critical conditions should be available within five days of life.
4. All NBS results should be available within five days of collection.

The DACHDNC charged the Subcommittee with outlining the NBS system, investigating existing gaps and barriers in NBS systems, identifying best practices to achieving these goals, developing a list of critical conditions that require urgent follow-up, reviewing the recommendations in light of new technologies, and suggesting revisions, if needed. The Subcommittee convened a work group to undertake this work. To date, the group has developed an outline of the NBS system; developed a focus group discussion guide; conducted focus groups at two regional collaborative meetings; and developed and conducted, in cooperation with APHL, a survey of states (using the themes identified through the focus groups as a starting point). Additionally, the work group held discussions concerning critical conditions with SIMD and is currently in the process of convening meetings with expert groups representing endocrinologists, immunologists, and pulmonologists. Other organizations to which the work group is reaching out include the Joint Commission and the American Association of Hospitals.

Dr. Kelm shared two diagrams with the Committee members. The first illustrated how all of the NBS system partners interact and the second illustrated the somewhat linear NBS process from parent education to follow-up, all of which is undergoing a continuous process of quality improvement.

With regard to developing a list of critical conditions that require urgent follow-up, the work group focused on metabolic conditions, hemoglobinopathies, and endocrine disorders. It worked with SIMD to develop the list of metabolic conditions and with experts who contributed to the case definitions project on the hemoglobinopathies, endocrine disorders, and cystic fibrosis. The hemoglobinopathies experts did not believe that these conditions require urgent follow-up; therefore, they were not included in the list of time-critical conditions. The endocrinologists recommended that congenital adrenal hyperplasia should be considered time-critical (results within five to seven days) and that congenital hypothyroidism be considered time-sensitive (results within seven to 14 days).

During the previous day's LS&P Subcommittee meeting, Dr. Berry presented on SIMD's efforts to identify critical metabolic conditions. SIMD defined critical conditions as those "on the RUSP in which acute symptoms or potentially irreversible damage could develop in the first week of life, and for which early recognition and treatment can reduce risk of morbidity and mortality." The SIMD position statement also stressed the importance of maintaining appropriate collection standards, of having access to presumptive positive results as soon as possible, and of providing immediate referrals for appropriate evaluation and management. Because these conditions can present within the first hours of life, SIMD acknowledged that it is not always possible to have NBS results for these conditions before symptoms appear. SIMD also recommended that clinicians include IEMs in their differential diagnoses for sick newborns. The position statement also included several considerations related to clinical variability.

APHL Survey

Dr. Tanksley reported on the APHL's survey of states concerning gaps and barriers to NBS and actions taken to improve timeliness of collection, screening, and transit. The survey consisted of 31 questions divided into three sections on communication between state NBS programs and birthing facilities, on state NBS programs and the 2006 timeliness recommendations, and on new technologies and tests and how they have affected timeliness. APHL sent (by email) two versions the survey -laboratory and follow-up versions - to the public health laboratory director, the NBS laboratory director, and the follow-up coordinator in each state. States could respond to t one or both versions; however, APHL asked that the laboratory version be submitted if a state elected to submit only one version of the survey. APHL received 62 responses (47 laboratory and 15 follow-up) representing all 50 states and Puerto Rico.

With regard to communication between state NBS programs and birthing facilities, the survey findings indicated that all NBS programs provide regular feedback to birthing facilities concerning issues such as unsatisfactory specimens, transit time, and completion of essential information. All Fifty state programs provide technical assistance and training to NBS programs, typically on request or in response to specific issues. Thirty states have mechanisms, such as matching NBS samples to vital records/birth certificates, to ensure that all newborns in the state are screened. Barriers identified by the states included a lack of linkages between NBS records and vital statistics, failure to link to specific (i.e., Amish) populations and to home deliveries, lack of availability of birth certificate information at time of screening, and lack of mechanisms to capture parent refusals.

Dr. Tanksley reviewed the survey responses for each of the four DACHDNC timeliness recommendations, including responses related to factors having a major impact on NBS programs' ability to meet the goal, gaps and barriers, and to best practices.

State performance related to the first recommendation - initial NBS specimens should be collected at 24 to 48 hours of life - The median percent of NBS specimens collected between 24 and 48 hours of life was 82.2 percent. Factors rated as having a major impact on programs' ability to meet this goal included compliance with collection from premature and sick infants, transfers of newborns prior to collection, release of newborns prior to 24 hours, and high turnover of staff responsible for NBS collection. Gaps and barriers related to births in midwifery centers and other out-of-hospital births, lack of education, high staff turnover, and state regulations concerning collection timelines being out of alignment with the recommendation. Best practices related to education and outreach, monitoring performance and providing feedback, and making statutory or regulatory changes to match the recommendation.

State performance related to the second recommendation - NBS specimens should be received at the laboratory within 24 hours of collection.- ranged from a low of 0.6 percent to 80.8 percent of samples being

received within 24 hours of collection. The median was 25 percent of specimens being received within 24 hours of collection. States identified the major factors impacting their ability to meet this goal as geographic distance between birthing facilities and laboratories, laboratories not accessioning specimens over the weekends or holidays, laboratory and courier hours of operation, lack of a dedicated courier service, and batching of samples by birthing facilities. They also identified gaps and barriers in the areas of mail and courier services, birth facility challenges related to sending out samples, and lack of timely feedback from birthing facilities regarding performance. Best practices related to using courier services and overnight delivery services, providing educational activities to birth facility and laboratory staff as well as parents, conducting continuous quality improvement activities, and expanding NBS laboratory operating hours.

State performance related to the third recommendation - NBS results for time-critical conditions should be available within five days of life - APHL identified 37 states that differentiate conditions based on whether or not they are time-critical (the lower number of responses might be related to the lack of capacity to rapidly query their data systems for the information needed to respond). Conditions identified by states included those on the SIMD time-critical list as well as others that were not on the list. Only 17 states responded to the question concerning the percent of time-critical results that are available within five days of life, with reported percentages ranging from zero percent to 99 percent. The median reported percentage was 75.8 percent. Major factors affecting NBS programs' ability to meet the goal of the third recommendation related to receipt time of specimens (e.g., specimens received at five days of life), courier and laboratory operating hours, lack of reporting of home births, and second tier testing implemented to reduce false positives. Gaps and barriers were primarily related to delay in receipt of samples and the use of out-of-state laboratories. Best practices identified by the responding states involved expanding education programs for birthing centers on specimen collection and submission, expanding NBS program operating hours, using couriers or overnight delivery services, developing a quality improvement feedback loop for birthing facilities and couriers, and working to improve the overall NBS program process.

APHL received 22 responses to the questions concerning the fourth recommendation - all NBS results should be available within five days of collection. The median percentage of results meeting the goal was 81.9 percent. NBS programs reported that delays in the overall process, laboratory operating hours, test length, the ability to implement change, and release of paper records to submitters by postal service were the major factors affecting their ability to meet this recommendation. Limits within the laboratory itself or the laboratory information management system (LIMS) and delayed specimen receipt were the major barriers and gaps. Best practices were similar to those for previous recommendations and related primarily to expanded educational activities, timely specimen collection and transit, improved reporting and communications mechanisms, cross-training of laboratory staff, and continuous performance monitoring and feedback.

The third part of the survey addressed new technology and second tier testing. Nine states reported that the use of new technology or the addition of new screens improved their ability to perform timely NBS; 15 reported that they hindered their timeliness. Twenty-four states indicated that new technologies and/or tests did not affect their timeliness. Improvements came from the ability to continuously load test plates, equipment that requires minimal supervision, deployment of new computer systems, quicker results, and greater precision and accuracy. Factors that hindered timeliness included the increased number of disorders and resulting increase in testing time, higher reagent costs, limited resources and capacities, pressures to reduce false positives resulting in more testing, and delays in reporting due to second tier testing.

Dr. Tanksley indicated that there were several survey limitations. Lack of definition of terms caused some confusion and resulted in multiple interpretations of the timeframes in the recommendations. A lack of appropriate LIMS data fields (e.g., can collect date of receipt of samples but not time of receipt) hampers data collection. Software limitations make programs unable to quickly pull data in response to ad-hoc requests.

March of Dimes NBS Quality Improvement Activities

Dr. Dolan reported on the March of Dimes' NBS quality improvement activities. The NBS Quality Improvement Work Group, which is made up of 14 organizations, focuses on the culture of safety in NBS. This group has held two conference calls and an in-person meeting; another call is scheduled for October.

As part of its culture of safety efforts, the March of Dimes has established two sets of awards. The first awards are for state health officials who have set a target of having NBS screening results available within 72, 48, or 24 hours or who have put policies in place to have screening accomplished within these timeframes. The organization hopes that states will receive awards over time for decreasing the amount of time needed for results as they set and achieve benchmarks. The second award is the Robert Guthrie Newborn Screening Award. It will be given to the state health official who meets the highest screening goals. The first annual Guthrie award will be presented during the week of September at the March of Dimes' volunteer leadership conference. Nominations for the awards should be sent to Dr. Edward McCabe.

Dr. Dolan welcomed feedback from the Committee on the awards initiatives. She also expressed appreciation for the way in which the timelines between the various groups are lining up, which provides unity on the goals being set for states.

Revisiting the Recommendations

The Subcommittee's work group on timeliness developed recommendations concerning updates to the four DACHDNC timeliness recommendations, in light of the new data, and identified a new approach to the recommendations. The emphasis should be on the overall goal of the program. Recommendations 3 and 4 should be given priority, making the overall goals timely notification of presumptive positives and completion of all testing as quickly as possible. Recommendations 1 and 2 provide the means to achieve these two overall goals.

With regard to Recommendation 3 - NBS results for time-critical conditions should be available within five days of life.- Dr. Kelm stated that the definition of "available" was one of the key issues identified by the Work Group in its discussions concerning this recommendation. Timelines in this recommendation are too open to interpretation and require clarification. Additionally, data needs to be captured so that actual timeframes can be calculated to measure performance (it might not be possible to capture this data at this point in time given the existing systems).

The work group recommended new wording for recommendation 3:

> *Presumptive positive results for time-critical conditions should be reported to the child's health care provider within five days of life.*

The work group identified similar problems with the definition and interpretation of "available" as it is used in Recommendation 4 - All NBS results should be available within five days of collection. Similarly, timeframes need to be defined and data concerning the timeframes needs to be captured. The work group believed that it was important to distinguish between time-critical and time-sensitive conditions. The proposed revisions focus on providing any out-of-range results for time-sensitive disorders in a timely fashion and indicate that screening for these disorders in a timely fashion is also important. The revisions also point out the need to provide normal results in a timely manner.

The work group developed two new recommendations in place of Recommendation 4:

> *All presumptive positive results for time-sensitive conditions should be reported to the health care provider within seven days.*
>
> *All NBS results should be reported within seven days of life.*

The Work Group identified several considerations related to Recommendation 1 - Initial NBS specimens should be collected at 24 to 48 hours of life. There are different recommendations for the collection of

specimens from pre-term, low birth weight, and sick babies. Timeframes vary from state to state, with some states requiring samples be collected in as little as 12 hours and some requiring collection within 72 hours. Additionally, it is important to balance the risks for false negatives and false positives that could be affected by collection timeframes. The proposed new wording for this recommendation was:

> *Initial NBS specimens should be collected in the appropriate timeframe for the baby's condition, but no later than 48 hours after birth.*

Factors that affect NBS programs' ability to meet the timeframe set forth in Recommendation 2 - NBS specimens should be received at the laboratory within 24 hours of collection - include availability of/access to couriers, geographic challenges, severe weather, and batching and improper handling of specimens by the birthing facility. Routine second screens also create timeliness problems. Dr. Kelm indicated that there were more problems with data related to this recommendation than any of the others and that there are many parts of the system that must work properly to achieve this goal. The work group proposed the following new wording for this recommendation:

> *NBS specimens should be received at the laboratory ideally within 24 hours of collection but no later than 72 hours after collection.*

Dr. Kelm stressed that the new order of the recommendations first sets goals for the overall program and then provides two goals that support the overall goals.

Committee Discussion:

- In response to a question about how states report results, Dr. Tanksley explained that the majority of states have identified time-critical conditions; however, the survey did not gather information on how states handle these results.
- A Committee member expressed concern over the timeframes in the last two recommendations (i.e., no later than 48 hours and no later than 72 hours), which puts receipt at the laboratory at five days and does not allow time for testing and reporting of time-critical conditions within five days. The work group hoped that states would work toward meeting the lower range of the timeframes. Getting specimens to the laboratory in a timely fashion is the greatest challenge reported by states.
- A Committee member stressed the importance of developing standards for the final two recommendations.
- The second two revised recommendations (presumptive positive results and all results reported in seven days) seem redundant. Dr. Kelm indicated that some of the second tier testing requires longer timeframes. The difference is in how results are calculated. For the time-critical results, reporting is considered contact with the child's health care provider; for all of the other reports, reporting is considered a report being available (not the communication of the report). The issue is how the recommendations are worded.
- A Committee member did not believe the recommendations went far enough. NBS laboratories need to be open every day. The recommendations need to be stronger; presumptive positive results should be reported within four days and the recommendations should include one concerning public health laboratories being open every day. Federal agencies should provide funds to state laboratories to enable them to improve their processes, including opening daily, improving technologies, and expanding staffing.
- The work group should consider developing a recommendation concerning the need for a tracking and management system to support the implementation of the recommendations. NewSTEPs is collecting this information by working with vendors to include these measures in their systems as quality measures that are reported out annually. Additionally, there is interest in some states in collecting and tracking this type of information locally on a monthly basis.
- In response to a question concerning education and training, Dr. Kelm explained that these efforts were mostly for health care providers (e.g., birthing facilities). There are issues within health care facilities concerning awareness about NBS and why it is done. Education needs to be done frequently to address staff turnover. Dr. Carla Cuthbert described her recent outreach and

education efforts at the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) conference and the interest of the participants in sharing what they learned with their colleagues. The Clinical and Laboratory Standards Institute indicated its willingness to allow the sharing of its education materials through the nurses' networks.

- With regard to the types of training being provided that was identified through the survey, Ms. Careema Yusuf reported that training is conducted using online training manuals, annual meetings, and publications. Due to reduced resources, training is not as readily available as many would prefer.
- A Committee member observed that education is not generally sufficient to change behavior. Education is a first step, but feedback based on data is necessary.
- With regard to states that fail to collect samples within the recommended window, a Committee member indicated that some of these states collect samples too soon instead of too late. The work group discussed whether the recommendation should specifically address healthy newborns, but decided to indicate that the collection should be dictated by the condition of the child.
- The revised recommendations should clarify the difference between reporting a presumptive positive result as soon as it is obtained and reporting it no later than five days of age. The recommendation should acknowledge that positives could be reported before the rest of the results.
- Genetic Alliance has a partnership with AWHONN to educate nurses. Education should focus on barriers within and assumptions made by birthing facilities regarding sample collection as well as the importance of NBS and sample collection. Another set of recommendations and strategies could be developed from the education and training perspective to address issues at the ground level rather than the laboratory level.
- A Committee member observed that the recommendations were designed around outcome markers and goals rather than process issues. Courier and laboratory operating hours are the most common issues. He believed that the recommendations should address these factors.
- A participant noted that many of the issues discussed are system issues, not simply laboratory issues. If hospitals collect samples at the same time their courier is picking up, delays have already been built into the system. The recommendations need to take a multi-faceted approach that targets the whole system. Dr. Tanksley replied that the proposed recommendations are achievable but difficult. States have already made significant improvements in timeliness. The recommendations provide goals; if NBS programs can do better than the goals they should strive to do so.
- A participant questioned the wisdom of setting a goal of 72 hours or less after collection for laboratory receipt of samples and asked if that goal was based on the data collected. Dr. Tanksley indicated that the 72 hour goal came from an ACMG report, which provided the 24 to 72 hours through two separate recommendations.
- The Committee should focus on setting the goals and allow NBS programs to determine how to achieve them. The first two revised recommendations set the overall standard. A Committee member questioned whether the five-day timeframe used for the revised first recommendation would protect the vast majority of babies.
- Some of the conditions present at birth, others within hours of birth (up to72 hours). Many of these babies are already sick when the sample reaches the laboratory. The purpose of NBS is not to make a diagnosis for babies that are already sick; instead it is to confirm a differential diagnosis made by clinical evaluation.

Dr. Bocchini summarized the discussion by stating that the first three revised recommendations are acceptable to the Committee with an adjustment of the language. There was considerable concern about identifying a span of time, out to the maximum, rather than setting a standard that all programs should strive to achieve. By allowing a delay in the maximum time that a sample could be taken, the recommendation puts laboratories in the worst possible position as they have less time to achieve the primary goal of getting results out in five days. He recommended that the recommendations concerning collection and receipt of specimens be as specific as those concerning reporting results.

Dr. Kelm stated that the recommendations are a living document that can be changed over time. The DACHDNC is working with the March of Dimes and multiple other organizations to develop a consensus

on recommendations. Once consensus is reached, the organizations will approach the Joint Commission about developing recommendations for the hospital setting.

Dr. Greene recommended working with the Joint Commission to make the timely collection and sending of samples by the hospital a sentinel event. Dr. Bocchini indicated that the effort to approach the Joint Commission would be much stronger if the consortium of organizations working on these issues made a joint appeal.

The revised recommendations for timely NBS are –

In order to achieve the best outcomes for babies:

1. Presumptive positive results for time-critical conditions should be immediately reported to the child's healthcare provider but no later than the 5th day of life.
2. All presumptive positive results for time sensitive conditions should be reported to the healthcare provider within 7 days of life.
3. All NBS results should be reported within 7 days of life.

In order to achieve these goals (and reduce delays in newborn screening):

1. Initial NBS specimens should be collected in the appropriate time frame for the baby's condition but no later than 48 hours after birth.
2. NBS specimens should be received at the Laboratory within 24 hours of collection.

X. Electronic Standards for Public Health Information Exchange – National Committee on Vital and Health Statistics Letter to the Secretary

Walter G. Suarez M.D., M.P.H.
Executive Director
Health IT and Strategy and Policy
Kaiser Permanente Information Technology
National Committee on Vital and Health Statistics
Silver Spring, MD

Dr. Walter Suarez described the role of the National Committee on Vital and Health Statistics (NCVHS) and the recommendations it sent to the HHS Secretary.

NCVHS advises the HHS Secretary on health data, statistics, and health information policy and provides a forum in which public and private sector organizations can discuss issues related to health data and information policies. The Committee consists of 18 members who meet on a quarterly basis. The NCVHS' work focuses standards; population health; privacy, confidentiality, and security; health quality; and data access. In 1996, the Health Insurance Portability and Accountability Act (HIPAA) gave NCVHS the responsibility of advising the HHS Secretary on health data standards and privacy policy. The Medicare Modernization Act of 2003 further expanded the group's role to include recommending electronic prescribing standards. Most recently, NCVHS' role was expanded even more by the Affordable Care Act (ACA) to include recommendations on operating rules for HIPAA administrative simplification.

Public Health Information Exchange Standards
NCVHS focuses on standards that support the electronic exchange and interoperability of information needed to achieve core public health functions. These include bidirectional and multidirectional exchanges of information. Public health is one of the areas with which health care organizations must exchange records. Electronic health records (EHRs) help support the provision of high quality care to individuals, and exchange of information between EHRs is an essential part of this effort (e.g., coordination and transitions of care).

Sources for public health data include medical data for individuals collected in clinical settings during patient encounters, environmental data collected through monitoring systems and special projects, and survey data collected from a variety of sources. The rapid expansion of the use of EHRs has the potential to create a digital divide between the clinical world and public health systems. The public health infrastructure is currently based on multiple systems that support a variety of public health programs. The number and variety of these systems is a challenge for those working to integrate them. It also creates difficulties when trying to link data for individuals over time through various programs and geographic areas. There are efforts within the clinical world to improve integration of data. EHRs (including non-clinical sources such as laboratory health and pharmacy information systems) and administrative systems are the two most significant sources of information exchange with public health systems.

Dr. Suarez addressed some of the challenges associated with implementing standards, including the problems that arise when standards include much optionality. Optionality creates barriers to interoperability because it allows users leeway in their interpretation of the standard and results in implementation of many variations of the same standard. In the clinical world, standards for the exchange of clinical information with high levels of optionality are being adopted and are creating barriers for full interoperability.

Standards establish the message structure, format, content, coding, vocabulary and terminology, transport mechanism, security, and other elements that define how information will be exchanged. The goal is to move from sending unstructured messages (essentially print images that cannot be processed in an automated way) to a fully codified system of structured messages that can be read electronically. Other goals include linking public health and external entities and establishing bi-directional exchanges. Areas in which standards for exchange have been developed include vital statistics (e.g., electronic birth and death record systems), immunization data, disease registry systems, and public health laboratories. Dr. Suarez identified clinical decision support tools as one area in which significant work is taking place and which has the potential to more closely link clinical care and public health.

Dr. Suarez briefly reviewed the core national standards adopted by the Office of the National Coordinator for Health Information Technology (ONC) and some of the public health organizations that have supported their development. There are four vocabulary and code sets, as well as standards for content structure, transport, security, and service.

Challenges associated with the adoption of public health standards include the need for more data collection and reporting from clinical systems to public health systems, the need for internal workflows within organizations to support the collection and submission of data, limited government (all levels) participation in development efforts, funding limitations for standards testing and EHR initiatives, little to no EHR vendor engagement, the need to collect data from multiple data sources, and data that is in paper or other forms that cannot be processed not electronically.

NCVHS Recommendations

NCVHS held hearings on the state of public health information systems and standards in November 2013. The hearings engaged a wide range of stakeholders. They were intended to create awareness of the need to advance a public health information system across the nation. The information gathered during the hearings influenced the recommendations to the HHS Secretary. Major themes identified during the hearing were the need for sustained investment in the nationwide public health information infrastructure, the importance of identifying and optimizing common infrastructure and data analytic capabilities, the need for appropriate incentives for the adoption and implementation of public health standards, the need to improve the maturity and adoptability of standards for public health applications, and the need to increase workforce informatics competencies.

NCVHS developed five recommendations concerning the public health information system and standards:

1. HHS should pursue the development and implementation of a new National Public Health Information Infrastructure Strategic Initiative.
2. HHS should establish a Public Health Information Infrastructure Dedicated Fund jointly governed by CDC and a public health collaborative organization.

    a. HHS should leverage the Public Health Infrastructure Dedicated Trust Fund to provide sustained funding for continuous quality improvement for public health information systems; promote, develop, and sustain informatics skills of the public health workforce; and standards development and adoption.
3. HHS should work with public health community to establish a National Public Health Informatics Standards Collaboration Initiative to accelerate adoption and use of standards in public health programs.
4. HHS should leverage different policy programs and initiatives to align incentives; stimulate vendor engagement in adopting/using standards; ensure public health data requirements are incorporated into standards and clinical information systems; and identify, document, and share examples of the benefits of adopting public health standards.
5. HHS, in partnership with the public health community, should develop a new National Strategy for Public Health Informatics Capacity Building to increase the number of informatics-savvy, skilled professionals in the public health workforce.

The recommendations focused on the development of a national strategic initiative for the public health information infrastructure; this formed the basis for the first recommendation. The second recommendation promoted the establishment of a dedicated fund that could be used to support the first recommendation. The third recommendation encouraged collaboration among the many stakeholders to accelerate adoption and use of the public health standards. Leveraging policy programs and initiatives, such as the ACA and meaningful use, was the emphasis of the fourth recommendation. The final recommendation focused on building capacity to ensure that there is a sufficient, well-trained informatics workforce in the public health arena.

Committee Discussion:

- A few years ago, the DACHDNC recommended including a field in the national birth certificate that would link the NBS DBS. The recommendation was not accepted, possibly because of the structure of the birth certificate. Dr. Suarez believed that it would be possible to include such a field without creating disruptions in the structure of the certificate. NCVHS will take this issue under consideration in the coming year.
- In response to a question about responses to the recommendations and support from ONC, Dr. Suarez indicated that the recommendations have been well received by HHS leadership. The Office of the Assistant Secretary for Planning and Evaluation is looking into how best to operationalize the recommendations. ONC is also supportive of the recommendations.
- A participant stated that meaningful use would not be an effective way to move this forward as he anticipated a significant fall off in participation due to the difficulty of the current next level standards and the punitive nature of the audit process. He asked whether any of the information sharing could be done using a two-way approach that would allow the system to both receive information from primary care providers and alert them about patient needs based on public health issues (e.g., patients needing immunizations). Dr. Suarez agreed that meaningful use would be an increasingly less effective tool for promoting adoption. He also agreed that population health management is the next major transformational activity and will be critically important in supporting efforts to improve health. These capabilities need to be built inside the EHR system; analytic capabilities also need to be developed to be able to mine the data.
- One participant stressed the importance of leveraging existing public health standards and efforts instead of creating new standards.
- A participant recommended that the Committee give its support to these recommendations and continue to work with other groups on these efforts. The NBS formal use case was one of the initial activities in the National Health Information Infrastructure. He emphasized the need for point-of-care standards.
- A representative from the National Library of Medicine noted that the DACHDNC supported the standards for NBS, which uses conventional HL7 standards and conventional LOINC codes. Support for this should continue and not be displaced by support for something new. He was concerned that the emphasis would be on developing more standards for public health rather than supporting and implementing existing standards.

- A Committee member noted that research related to NBS, especially issues related to making data public, is an extremely sensitive issue for parents, families, and advocates. Much attention needs to be given to privacy and confidentiality before NBS is linked with birth certificates. Dr. Suarez indicated the NCVHS's subcommittee on privacy, confidentially, and security is looking into these issues as they relate to public health data linkages.

The Committee agreed that Dr. Bocchini would send a letter on behalf of the DACHDNC in support of the NCVHS Recommendations to the HHS secretary.

XI. Report: *Succinylacetone as Primary Marker to Detect Tyrosinemia Type 1 in Newborns and Its Measurement by Newborn Screening Programs*

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

During the previous meeting, the Committee accepted the LS&P Subcommittee's report, *Succinylacetone as Primary Marker to Detect Tyrosinemia Type 1 in Newborns and Its Measurement by Newborn Screening Programs*, and elected to send a recommendation to the HHS Secretary concerning efforts to educate stakeholders about the benefits outlined in the report.

In the interim, the following recommendation was developed:

> *The Secretary of Health and Human Services should facilitate a national dialogue among federal and state stakeholders on the benefits of measuring succinylacetone in dried blood spots to improve the specificity of newborn screening for Tyrosinemia type 1, a condition on the Recommended Uniform Screening Panel.*

The Committee discussed which groups would be considered stakeholders (e.g., laboratories, state NBS programs) and whether they should be more specifically identified. Dr. Bocchini indicated that the stakeholders would be defined in the letter to the Secretary that transmits the recommendation.

Dr. McDonough made a motion to accept the recommendation and send it to the HHS Secretary. Dr. Thompson seconded the motion. The Committee members present voted unanimously to accept the recommendation.

XII. Follow-Up and Treatment Subcommittee Update

Charles Homer, M.D., M.P.H.
Subcommittee Chair
Chief Executive Officer and President
National Initiative for Children's Healthcare Quality
Boston, MA

Dr. Homer briefly reviewed the Follow-Up and Treatment (FU&T) Subcommittee's charter, which tasks it with identifying barriers to post-screening implementation and short- and long-term follow-up, developing

recommendations for overcoming those barriers, and developing guidance on the responsibility for post-screening implementation and short- and long-term follow-up.

In support of a priority related to real-world impacts and outcomes, the Subcommittee chose to explore the extent to which improved clinical outcomes can be documented to determine whether NBS is achieving its intended purpose. This effort included an evaluation of the impact of variability in clinical care. These efforts led to the creation of a framework for assessing the outcomes of NBS which was described in the paper titled *A Framework for Assessing Outcomes from Newborn Screening: Do We Know if We Are Achieving the Promise of NBS?* The paper defined survival and well-being as the key outcomes and identified four critical outcome drivers: rapid and reliable diagnosis, evidence-based therapeutic and rehabilitative care, coordination and integration for services, and continuous improvement and knowledge generation. The Subcommittee developed measures that reflect the four drivers for sickle cell disease and PKU.

During the previous meeting, the DACHDNC tasked the Subcommittee with exploring ways to further operationalize the framework. In support of this task, the Subcommittee will identify the extent to which public health programs and clinical delivery systems are employing elements of the framework and whether they are using the resulting data to improve care. The Subcommittee plans to work with the regional collaboratives to determine which states have LTFU systems in place and identify barriers to widespread implementation of LTFU systems.

For those states that have LTFU systems in place or are developing promising systems, the Subcommittee plans to assess their capacity to implement the framework, identify lessons learned from their implementation efforts, and consider how this type of capacity could be expanded to other programs. Subcommittee members discussed the importance of not losing focus on the potential of systems under development as it studies what is currently in place and the need to connect to and accelerate the adoption of the Longitudinal Pediatric Data Resource.

Dr. Homer stressed that the purpose of the framework is to use measurements to drive improvement. Subcommittee members are aware of the importance of not focusing exclusively on measurement but on focusing on the use of the data to produce better outcomes. The Subcommittee is also aware that its broader charge is to identify and address barriers to long-term treatment, which includes the supply of and access to appropriate care and expertise.

The Subcommittee set up a work group to identify states that are using or planning to use the elements of the framework.

Committee Discussion:

- A Subcommittee member added that the group discussed potential connections to the NCVHS letter on standards and possible sources of funding for implementation of standards and pilot projects. The Subcommittee plans to work on identifying ways to interface the REDCap database with existing EHR systems. The Subcommittee also plans to focus on identifying the most valuable data elements for collection in a resource-limited environment.
- The framework has not yet been published, which will make it difficult to determine how states have implemented it. Rather, the Subcommittee should assess what states are doing already and how it fits into the framework.
- A participant reminded the Subcommittee members about the work on LTFU in the states presented to the DACHDNC about one year ago by Dr. Beth Tarini. This work could inform the current effort.
- The framework was meant to be tested to determine whether the fit is appropriate; however that determination has not been made. A participant was concerned that expanding it to other diseases might be premature. She believed that by more fully testing the framework using the two initial conditions, the Subcommittee would find that programs have a long way to go to have LTFU. The underlying goal is not to tell states what they should do with the framework but rather to structure an environmental scan to help identify weaknesses and opportunities.

- The framework, as approved for publication by the Committee, does not set any specific measures or goals; instead it provides examples of measures that could be used. Potential Subcommittee projects could involve having states test the framework to determine whether it helps them understand what is actually happening. Additionally, the Subcommittee should keep in mind that there are other ways to look at access issues besides the framework.

XIII. Education and Training Subcommittee Update

Catherine A.L. Wicklund, M.S., C.G.C.
Subcommittee Chair
Center for Genetic Medicine
Feinberg School of Medicine
Northwestern University
Chicago, IL

Ms. Wicklund reported that the Education and Training Subcommittee is currently completing several of its priorities.

Priority A: Track, Provide Input on, and Facilitate Integration of National Education and Training Initiatives
Work under Priority A included a project to identify heritable conditions that are not currently part of the RUSP and for which screening and treatment would be most likely to occur at a later point in development. This project highlighted that the Committee's role is not limited to NBS but includes a wide range of heritable disorders. During the previous meeting, Dr. Tarini summarized the Subcommittee's work on three exemplar conditions. The Committee requested that the Subcommittee frame its findings so as to highlight barriers to conducting population-based screening for these types of childhood conditions. Dr. Tarini developed a two-page summary of the findings, which addressed the inability of states to conduct population-based screening and of the role of public health versus simply having practice guidelines. The Subcommittee needs to review the summary in preparation for presentation to the Committee. Dr. Tarini and Dr. Bailey will discuss the possibility of developing a white paper or article based on the project findings.

Priority B: Promote Newborn Screening Awareness among the Public and Professionals
Ms. Wicklund reported that activities under this priority are complete. Activities focused on supporting ongoing CDC education activities.

Priority C: Provide Better Guidance for Advocacy Groups and Others Concerning the Nomination and Review Process.
This priority encompassed two projects. The first project is the development of a public-friendly document describing the DACHDNC nomination process. The Subcommittee has discussed this effort with the CRW, but has not yet begun work on it. The National Newborn Screening Clearinghouse, which is maintained by the Genetic Alliance, is also working on this initiative. Next steps under this project include tracking the work being done by Genetic Alliance and identifying ways the Subcommittee can support its work.

The Subcommittee is also developing a glossary of terms to help those interested in the nomination process. The glossary includes terms used in the nomination form. Currently, the Subcommittee is working to ensure that the glossary is at an appropriate reading level (sixth grade). The hope is that the glossary will help advocates better understand the information that needs to be submitted as part of the nomination process. Next steps include determining whether it will be possible to post the glossary to the DACHDNC website.

Preliminary Needs Assessment
Since many of the Subcommittee's projects are complete or nearing completion, the Subcommittee conducted a preliminary needs assessment by considering a series of questions concerning the most

important issues in NBS and in NBS education and training, the current status of NBS, and the most significant obstacles to NBS and NBS education and training. Some of the themes that emerged during the discussion related to:

- Points in the system where the most serious issues arise
- The challenge of dealing with rare conditions and educating stakeholders
- Education about and impact of false positives on parents
- Infrastructure issues, including state health departments being overwhelmed, lack of funding, vulnerability (DBS storage issues and negative perceptions), and information technology needs
- General education issues, including identifying key messages and engaging parents to help educate other parents
- Primary care provider access to specialists, including other models that can be applied to NBS
- Timeliness issues
- Workforce issues, including access to medical geneticists
- Education regarding exome and genome sequencing

In considering the various needs, the Subcommittee members were mindful of identifying areas in which its efforts could have the most impact as well as being careful to avoid duplicating other groups' efforts. The Subcommittee was also concerned that any future work focus on all heritable disorders, not just those identified by NBS. Dr. Wicklund indicated that the Subcommittee needs to put more thought into potential projects and welcomed input from the full Committee.

Committee Discussion:

- With regard to Priority A, a participant noted that practice guidelines might not be the best way to inform those involved in service delivery; the Subcommittee should consider other ways to effectively educate those providing services.
- With regard to Priority A, a Committee member noted that developmental screening for autism, which is a parallel for childhood screening for heritable disorders, is in the public health domain. The Title V programs are interested in taking steps within public health to support practitioners in implementing clinical guidelines. Dr. Bailey indicated that the Subcommittee's original interest was determining whether there would be any value in later population screening.
- The discussion highlighted the issue of the Committee's role with regard to diagnosis and early intervention for heritable disorders versus its role with regard to the broader picture. A Committee member noted that many states are reconfiguring their systems for managing complex, chronic illnesses; these decisions could result in children being put into care systems that are unfavorable to them. She asked whether the Committee has a role in addressing broader issues such as access to care and health care financing.
- Another Committee member agreed that issues of access to care as part of LTFU are very important and that any work on this should fall under the FU&T Subcommittee.
- The increase in prenatal screening raises issues for NBS including education for parents and clinicians, how to get information from the prenatal period into the NBS period and beyond, and bioinformatics. The Subcommittee needs to take prenatal screening into account as it looks at the continuum of care.
- Implementation is a multi-faceted process. If the Subcommittee decides to address implementation, it should be aware of the complexity of the topic. There were concerns that the Subcommittee members might not have the requisite expertise to undertake the topic.
- Training plays an important role in helping people and systems understand why genetic counselors are an important part of the care team.
- Dr. Homer stated that it is not always clear to what extent the Committee is an advocacy group. Dr. Bocchini stated that the DACHDNC is a policy committee. Its goal should be using the expertise of its members to develop the best policies for children and families. Part of fulfilling this goal includes identifying gaps and recognizing opportunities for study. Using the framework developed by the FU&T Subcommittee to study the effectiveness of LTFU and treatment for a particular condition is an appropriate activity for the Committee.
- Although the subcommittees meet independently, there is some overlap in the topics they address. In the future, thought should be given to providing opportunities for subcommittees with

overlapping interests to share information and coordinate activities. Dr. Bocchini indicated that the subcommittee chairs have met by conference call to share information on their subcommittee's activities.

- There are opportunities for the Committee to explore roles and responsibilities with regard to LTFU, specifically what is happening and how it is happening.
- The evolution in health care has resulted in a system that ignores the exceptional patient in order to save money and provides lots of care to those with common, lifestyle problems. This approach does not work well with the family-centered medical home, which involves personalized care. While the Committee cannot advocate, it can identify barriers. The framework was developed to help identify barriers to follow-up and treatment. A Committee member recommended that the DACHDNC continue to study LTFU, transitions of care, and how those with exceptional needs can be served within these new systems.
- A participant observed that there is an opportunity for education concerning later-onset diseases.

XIV. Future Topics

Dr. Kelm stated that the Food and Drug Administration (FDA) notified Congress that it intends to release draft guidance that indicates a framework for regulating laboratory-developed tests. Nobody would be forced to use kits. As part of developing the guidance, FDA will assess what is on the market. This could result in some tests coming before FDA for approval. The draft guidance includes protections for tests for rare diseases.

Dr. Bailey noted that the centers that received funding to look into whole genome and whole exome sequencing have been in operation for about a year and recommended that a report be prepared for the Committee on the research being done by these centers.

Dr. McDonough reported that his organization has seen several children with critical congenital heart disease (CCHD) who had normal O2 saturation screenings in the hospital. These children had a coarctation of the aorta, which is not one of the conditions for which the screening was designed. He was concerned that providers assume that the O2 saturation screening picks up most cases of CCHD and expressed his interest in learning more about the current recommendations for clinically screening newborns for these types of conditions within the first three to seven days of age. Any proposed recommendations would be directed toward primary care providers, not the public health system. Dr. Greene observed that coarctation is not a cyanotic condition and might not be picked up by a second screening.

Dr. Greene indicated that she would like to hear a presentation on the effects of the ACA on children with rare, complex disorders.

XV. Adjournment

Dr. Bocchini thanked all of the attendees for their participation in the meeting.

The next meeting of the DACHDNC will take place on February 12-13, 2015.

With no additional business to address, Dr. Bocchini adjourned the meeting at 2:21 p.m.