Discretionary Advisory Committee on Heritable Disorders in Newborns and Children

Summary of 3rd Meeting
January 16-17, 2014
Webinar

Please note: These minutes are pending formal approval by the Committee. Corrections or notations will be incorporated into the final minutes.

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I. Administrative Business: January 16, 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

Dr. Joseph Bocchini welcomed webinar participants to the third meeting of the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC). Ms. Debi Sarkar, the Designated Federal Official (DFO), also greeted Committee members and organizational representatives.

Dr. Bocchini informed participants that the reauthorization of the Newborn Screening Saves Lives Act won unanimous approval from the Senate Health, Education, Labor and Pensions Committee. The bill proposes to amend the Public Health Services Act to extend and improve programs at the Department of Health and Human Services related to newborn screening and reauthorizes this Advisory Committee. The bill also makes timeliness of sending newborn screens a key component. It now moves to the full Senate for consideration. Action is still pending in the House.

Ms. Sarkar provided reminders to Committee members about appropriate constraints on their lobbying activities and interactions with the media and the public on questions about the Committee. She also informed participants that the next meeting will be a face-to-face meeting. Details regarding that meeting will be forthcoming.

Voting members present were:
Dr. Don Bailey, Dr. Bocchini, Dr. Jeffrey Botkin, Dr. Coleen Boyle (CDC), Dr. Denise Dougherty (AHRQ), Dr. Kellie Kelm (FDA), Dr. Charles Homer, Dr. Fred Lorey, Dr. Michael Lu (HRSA), Dr. Stephen McDonough, Dr. Dietrich Matern, Dr. Melissa Parisi (NIH), Dr. Alexis Thompson, Ms. Catherine Wicklund, Ms. Andrea Williams, Ms. Debi Sarkar (DFO)

Non-voting organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Frederick Chen
- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- American College of Obstetricians & Gynecologists: Ms. Mindy Saraco
- Association of Maternal & Child Health Programs (AMCHP): Ms. Kate Taft
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State & Territorial Health Officials (ASTHO): Dr. Christopher Kus
- Department of Defense (DoD): Dr. Adam Kanis
- Genetic Alliance (GA): Ms. Natasha Bonhomme
- March of Dimes: Dr. Edward McCabe
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society of Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

B. Committee Correspondence

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

Dr. Bocchini referred participants to the response from Secretary Sebelius to the Committee's recommendations regarding the retention and use of dried blood specimens after newborn screening. The Secretary declined the first four of the DACHDNC's recommendations and accepted the remaining four recommendations based on the Committee's report, the Interagency Coordinating Committee on Screening in Newborns and Children (ICC) review and the pending revisions to the Common Rule which stipulates protections for human subjects in research.

C. Approval of September 2013 Meeting Minutes

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

The Committee approved the minutes of the September 2013 meeting.

II. Update from the Sickle Cell Disease and Screening for Trait in Athletes *Ad Hoc* Workgroup

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

Dr. Thompson reviewed the questions which the Ad Hoc Workgroup addressed. These included:

- Are DACHDNC's recommendations in the White Paper to the Secretary still relevant?
- Is this approach an appropriate use of newborn screening resources?
- Is the DACHDNC able to provide additional guidance to the Secretary and/or to the state agencies?
- What is the impact of this experience on the broader discussion of notification of carrier status for other conditions?

In June, 2011, Secretary Kathleen Sebelius accepted four recommendations from the SACHDNC. Those recommendations were as follows:

1. Individuals should have the opportunity to find out their risk of medical disorders, including carrier status for sickle cell disease.
2. Evaluation should take place in the medical home and should include counseling and assurances about the privacy of genetic information.
3. Genetic testing should not be a pre-requisite for participation in sports, unless deemed medically necessary.
4. As part of routine medical care, all potential athletes should be given education of safe practices to prevent exercise and heat-related illnesses.

The above recommendations originally applied to Division I schools. By summer of 2013, the NCAA had put this mandate into effect for Divisions, I, II, and III schools.

Conclusions of the Ad Hoc Workgroup Regarding the Questions Reviewed

There was consensus among members of the *Ad Hoc* Workgroup that the SACHDNC's recommendations to Secretary Sebelius in 2010 are still relevant and valid. No changes were proposed.

Dr. Tarini presented to the *Ad Hoc* Workgroup information from stakeholders in states regarding sickle cell trait. Information provided by states is highly variable. Some states provide very detailed information on the entire newborn screen results with all of the tests which were performed. Some states are trying to provide additional

educational materials. However, it is not clear if states generally provide any information besides the original test results. Some states report anecdotally that efforts to provide additional information were rebuffed by universities.

The need for a disclaimer was discussed since this was not necessarily the intent of newborn screening and there was little discussion of the risk of false positive and false negative results. Nor was there a clear communication about screening versus diagnostic testing. Accuracy of test results was also discussed in addition to ensuring the test results are accurately matched to the correct individual who is currently requesting the results.

The *Ad Hoc* Workgroup also considered whether or not this is an appropriate use of newborn screening resources. Dr. Tarini provided information on the cost and burden to the states in order to meet these requests which are necessitated by the NCAA mandate. The Workgroup raised the issue of whether or not this is consistent with the intent of newborn screening if the results are provided without context. It is recognized, however, that newborn screening is often driven by public policy and health legislation in the states and there is much variation among states. Therefore, any variations to their current practices might require new legislation which can take quite some time.

The Workgroup considered what recommendations, if any, might be offered if the states regard this as a reasonable use of newborn screening resources and how the Workgroup might assist in developing such recommendations. A related question then arose regarding to whom this information would be given. Many of those with sickle cell trait are now young adults. The requests often come from parents or from third parties neither of whom would be given access to this type of health information without a clear reason why the individual himself/herself is not making the request. When that information is provided as part of the screening test results, are there other resources which states or individuals could be directed to utilize to provide the best current information on health concerns associated with sickle cell trait.

Educational Resources on Sickle Cell Trait
Althea Grant, Ph.D., updated the *Ad Hoc* Workgroup on some educational efforts of the Centers for Disease Control (CDC). The CDC is developing a Sickle Cell Trait Education Toolkit representing the products of several workgroups composed of hematologists and representatives from community-based organizations, the NCAA, the National Athletic Trainers Association and government partners. It provides general information as well as information on complications and issues related to sickle cell trait and participation in athletics. This Toolkit content will be vetted by the American Society of Hematology and the Sickle Cell Disease Association of America. It is anticipated that the Toolkit will be available by the spring of this year for downloading from the CDC website.

Workgroup's Conclusions
- The Workgroup agreed that the SACHDNC recommendations should stand.
- The Workgroup agreed that late requests for NBS results in response solely to the NCAA mandate are not an appropriate use of newborn screening resources.
- The Workgroup will further study how the DACHDNC might provide additional guidance to the Secretary and/or the states.

Next Steps
- The Workgroup would like to gather additional information from the states including the following:
    - Clarify current guidelines from each state on carrier notification as well as information about how that guideline was developed, e.g. in response to health legislation, developed internally, etc.
    - Ascertain what, if any, disclaimer about the results is provided.
    - Determine what, if any, educational information is provided with the results.
- The Workgroup would like to articulate the concerns raised by the NCAA mandate, perhaps in a report to the larger Committee. This report could eventually be configured into a paper.
- The Workgroup would like to consider possible mechanisms by which the DACHDNC could assist states.

Discussion

- Committee members expressed full agreement with the Workgroup's proposed approach and provided some questions and comments.
- One participant commented that the NCAA mandate was developed in response to a legal case and asked if there is a possibility that the NCAA may change that mandate or enter into a discussion given this information? The challenge has been that this was a legal settlement the terms of which were not made public. The NCAA has not said that this is their restriction. The mandate is clearly in the spirit of what the family in the legal settlement wanted, but it is not clear that there was an absolute requirement for the NCAA to carry out the settlement in the manner in which it has been done.
- Dr. Greene stressed that it is important to keep working on the issues related to the carrier testing requirement separate from the issue of newborn screening. It may be possible in time to stop the request to the newborn screening laboratories because the screening test result is not a diagnostic test. The Workgroup discussed some strategies which might help to make that clear. The CDC may include that information in their statement. APHL is considering strategies to guide public health laboratories in providing disclaimers. Hopefully it will quickly become clear that no one should act upon newborn screening test results without confirmatory testing. The other questions still remain, however, and this is a Committee on heritable disorders, not just newborn screening. Dr. Thompson agreed and added that APHL has always been a partner to this larger Committee. Their role is vitally important in helping state laboratories configure their responses.
- Dr. Matern commented that several states including Minnesota will no longer have that information from the newborn screening laboratory so you will have to go to the birth place in order to ascertain the newborn screening test result. That should be considered as true for other states, too. Texas had to destroy all their samples, but it is not clear what their process is at this point. Dr. Thompson agreed and added that in some states the newborn screening programs are relatively recent so those picked up by newborn screening are not yet eighteen years old. The most notable example is the state of Georgia. As individuals recognize that the states cannot be used as a resource for responding to that mandate, it will not mean that the NCAA will not continue to ask for it. This is a different, but related issue.
- Ms. Bonhomme commented that in addition to thinking of mechanisms by which we can support and assist states there are other organizations and groups such as community-based organizations, birthing hospitals, organizations that support the sickle cell community and organizations that do newborn screening education that will be asked questions related to this issue and we should keep that in mind. We need a multifaceted approach. People may not be going to their state laboratories for this information. They may go elsewhere including the pediatrician's office. We need a well rounded approach. Dr. Thompson agreed and added that the materials being developed by the CDC will be the most commonly distributed information. The CDC has a standing relationship with the American Academy of Pediatrics and this is the kind of thing for which the CDC will partner with the AAP.
- Dr. Boyle agreed with the point to unify the message across various venues. She asked for clarification about the first point under "Next Steps," i.e. to gather more information from states pertaining to understand their current guidelines for carrier notification, etc. She asked if the Workgroup sees that as a function of this Committee or how they envision that being done. Dr. Thompson responded that it will be necessary to ascertain whether there are resources available to use in gathering that information. This was beyond the purview of the work that Dr. Tarini had already been charged with doing, but this was a question for which the Workgroup needs input from the broader Committee. The Workgroup would hope to get some central resources to gather information from the states. Her expectation is that this would be a series of emails and/or calls that would eventually end up being organized into a spreadsheet and not much beyond that. However, this would require some staff time. Dr. Boyle then asked if the Workgroup sees the result of that effort being recommendations or Best Practices or something similar.Dr. Thompson replied that she does not know yet. The Workgroup is trying to figure out what the states are doing. Most are doing the best they can. But the Workgroup is trying to understand how broad that experience is. Perhaps states are already using their very good resources for information or have already made decisions regarding how they will handle requests for results, but we just don't know at this point and we would like to understand that.
- Dr. Botkin commented that there may be an opportunity as we look at the trait issue to gather information on how states are dealing with carrier status more broadly. Perhaps that is too tangential to the primary focus of this effort, but there are persistent questions about how carrier status is being communicated back to the primary care providers and families, the adequacy of that information, how people are responding to

that information. That is a long standing issue in the newborn screening field. This particular focus may offer an opportunity to look at the carrier status situation a little bit more broadly. Dr. Greene concurred with Dr. Botkin's point and again reiterated that a screen is not a diagnostic test. Nobody should be making decisions about athletics based on a screen; you don't even know if that was the right person or if the screen was negative the person could still have a hemoglobinopathy. If the screen was positive it could have been a false positive. Whatever states are doing, Dr. Greene is interested in the question of how we handle carrier testing, but whatever the states are responding it should be the same if it's the birthing center or the pediatrician: The newborn screening result does not tell the NCAA what they need to know; it is not a diagnostic test. The state should not be asked, the birthing center should not be asked and if the pediatrician is asked he/she should not be asked about the newborn screening report.

- Dr. Kus asked if the NCAA mandate affected any athlete, specifically, has any athlete refused to provide the information and then not been allowed to play? Dr. Thompson replied that that question has been raised but the NCAA has not come forth with answers. However, in the beginning when this mandate just applied to Division I schools, in one set of schools 90%of the students opted-out. We have asked repeatedly what information or methods those schools are using which results in this mass opting-out versus the message at schools that require that students be tested. We are trying to go through other channels to get the NCAA to talk with us and provide more information, but currently they are not responsive. Another participant asked if there is no information at this point from athletes themselves on issues that may have arisen based on results of the test? Dr. Thompson answered that the only information we know is that there have been no deaths.

Action Item

- Dr. Alexis Thompson solicited volunteers from APHL or from state NBS programs to join the *Ad Hoc* Workgroup. Volunteers are asked to contact Debi Sarkar.

III. Challenges with Conducting NBC Pilot Studies and Possible Solutions

Jeffrey R. Botkin, M.D., M.P.H.
Professor of Pediatrics and Medical Ethics
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The process of making recommendations about inclusion of conditions on the RUSP is vastly improved. The RUSP includes evidence-based conditions. The evidence-based approach that the DACHDNC uses in providing advice on the uniform screening panel is a major contribution to the field. However, we are dependent upon the quality of the data that have been generated within the system broadly in order to make those recommendations. We would like better quality information. We struggle with data that are, in many circumstances, marginally adequate. We know data are difficult to acquire and in this domain data acquisition is complicated since we are dealing with population screening and with uncommon conditions with which many clinicians are unfamiliar.

The evidence includes a number of elements such as the test characteristics in the context of a population screening. Once you get to the volume and required rapid turnaround times, it is an educational experience to see what challenges emerge with any particular test platform. Another point about evidence concerns the natural history/spectrum of the condition. Population screening typically yields positive results on a wider spectrum of the clinical condition than may have been previously recognized through clinical diagnosis. Thirdly, it is important for the process to demonstrate that early detection and intervention have a positive impact on child morbidity and mortality.

Research in this public health domain requires collaboration with State Departments of Health which can be challenging since many State Departments of Health do not consider research to be part of their mission and under certain circumstances some types of research are prohibited. Another challenge for research is the variability among Institutional Review Boards (IRBs) in expectations for human subject protections.
Dr. Botkin noted that related to this topic, a paper will be coming out in the February 2014 issue of *Pediatrics*. The paper is a collaborative effort of the Ethics and Legal Workgroup of the Newborn Screening Translational Research Network that deals with parental permission for pilot studies. A number of states such as Massachusetts and

Wisconsin have collaborated with investigators to conduct valuable newborn screening research studies. This type of work has been critically important for this Committee. A number of states, however, have been unable to support research projects. The Spinal Muscular Atrophy project has been hampered by states that initially supported the project at the time of grant application, but after a multi-million dollar grant was awarded states decided they had challenges in supporting that project. These barriers among others are factors in states deciding to implement new tests via state mandate rather than through an evidence review process. That is a reflection of an older style of newborn screening that ought to be inhibited. An evidence-based approach which has been used by this Committee is preferable.

Proposal
Dr. Botkin proposed that the DACHDNC may have a role in thinking through these issues and in making recommendations to the Secretary. The initial concept might be based upon state-based programs that are organized into a national network to conduct research when authoritative committees such as this one decide that a pilot study is necessary in order to make a decision on including a new condition in the platform. These ideas could be discussed in further detail at our next meeting. Activity is ongoing in the field to address this particular set of issues. The DACHDNC may be in a position to be informed about what is happening and may play a constructive role.

Discussion:

- Dr. McDonough expressed full support for Dr. Botkin's proposal and hoped that the DACHDNC would also support it.
- Dr. Bailey agreed with Dr. McDonough's comments and thanked Dr. Botkin for his discussion of a critical need. Dr. Bailey would further like to understand how Dr. Botkin would propose that the Committee would follow-up on his proposal in-between meetings in addition to talking to Dr. Watson and the Translational Research Network. Additionally, in the future, instead of doing tests on a single disease in state-wide pilot studies perhaps we ought to bundle more things together in order to get more for the same cost in a single study.
- Dr. Homer commented that this is a tremendous idea. He urged that thought be given to what type of coordinating center would be needed as well as the type of data infrastructure and how some newer forms of information exchange might be utilized.
- Dr. Parisi commented that this is a great idea and there is some infrastructure in place through the Newborn Screening Translational Research Network that could provide support to these pilot studies. Future developments should include the role of some existing structures that are already in place that could provide support. This is an important idea, but we don't want to have to "reinvent the wheel, either."
- Dr. Greene commented that SIMD will fully support this and perhaps there will be an opportunity for NIH to assist in this effort. A related issue is how to work across IRBs. It took over one year to get IRB approval in just three states to interview people for follow-up. The IRB component is important in this initiative.

Next Steps/Follow-up

- Dr. Bocchini concluded that Dr. Botkin's proposal and participants' comments give the DACHDNC some direction. At the next meeting, the DACHDNC could review existing structures and work with Dr. Parisi and others to ascertain what is available. They could hear more from Dr. Botkin and perhaps develop a Workgroup within the DACHDNC to bring this forward in some way.

IV. Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs)

Marci Sontag, Ph.D.
Associate Director of NewSTEPs
Colorado School of Public Health

Jelili Ojodu, M.P.H.
Director, Newborn Screening and Genetics Program

Association of Public Health Laboratories
Silver Spring, MD

Mr. Ojodu provided background information on the Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) which is funded through a cooperative agreement to APHL from the Maternal and Child Health Bureau/HRSA. NewSTEPs is a comprehensive newborn screening resource center especially for state newborn screening programs. It provides a publicly available website with information such as state profiles and case definitions (which will be added in the near future) and also serves as a data repository with varying levels of access for the public, state-run screening programs and public health decision makers. The mission is to "achieve the highest quality for newborn screening systems by providing relevant, accurate tools and resources and to facilitate collaboration between state programs and other newborn screening partners."

The goals of NewSTEPs are the following: Information gathering, building relationships; Education, networking; Data repository; Technical assistance. The organization strives to build the trust it has established with large, newborn screening programs, especially state newborn laboratories. They remain involved until the point of short-term follow-up, if not later. The organization works at regional, local and state levels in its education and networking activities. Being a national data repository is a key goal. They have built and validated a system of newborn screening, quality improvement activities and monitoring systems, quality indicators have been developed for application to the types of data collected for the data repository. The organization further strives to address needs of newborn screening programs and provide state newborn screening programs in maintaining continuous quality improvement. Finally, technical assistance is provided to newborn screening programs via education, training opportunities, working directly with those in newborn screening programs with their needs with pre-analytic, post-analytic activities up to the point of short-term follow-up. The organization works with states to address deficiencies in these areas and also shares Best Practices in place in some programs across state newborn screening programs.

Mr. Ojodu provided an overview of the NewSTEPs organizational structure, acknowledged new STEPs Staff and their respective roles and covered the roles of those on the NewSTEPs Steering Committee which is divided into five Workgroups as follows: Quality Indictors; Data Repository; Website; Evaluation Tool; Technical Assistance Workgroups (STFU and CCHD) plus a new, sixth category of the Health Information Technology Workgroup. Key among NewSTEPs activities are the following: Partnerships and outreach; Site visits; Quality indicators; Case definitions; Website and data repository; Disease specific activities; Continuous quality improvement.

Dr. Sontag elaborated on the goals of NewSTEPs. In terms of the goal of information gathering and building relationships in the cooperative agreement, the organization strives to identify gaps and barriers in newborn screening education across public health leaders and newborn screening programs' personnel. They also identify gaps and barriers in communication pertaining to new disorders, new assays and follow-up strategies. They also look at gaps and barriers in data collection and reporting as well as continuously working to build trust and strengthen their relationships among local, state, regional and national newborn screening stakeholders, private partners.

In terms of program evaluation and community input, NewSTEPs has sought information on quality indicators for newborn screening which were developed by the community; case definitions; newborn screening data use to understand how best to use the data and provide information back to the state programs and, finally, newborn continuous quality improvement for newborn screening systems throughout the nation. The organization has researched key components it will need for a newborn screening evaluation tool. They have also been involved in specimen transport issues to see how they can best support states to shorten specimen transport times. NewSTEPs conducted a series of interviews with Title V Directors across the country to ascertain their understanding of newborn screening and how newborn screening systems interact with Title V programs. All states are participating now in some manner and the organization will solicit their feedback on how NewSTEPs can help them with their work.

The second goal of education, networking is being carried out, in part, by creating and supporting a newborn screening network for education and communication at the local, state and national levels. It is recognized that

networks of individuals working together can improve newborn screening outcomes. NewSTEPs does in-person networking as well as virtual networking via webinars to share successes and challenges.

The interactive website at www.newsteps.org is a key part of the education program at NewSTEPs. The website is geared to separate audiences: Parents and caregivers, policy makers and administrators. Information will continuous be added to the website. The number of hits on the website continues to increase since it became available in May, 2013.

Other educational outreach activities include two follow-up workshops each with eight attendees. Those workshops will continue to be offered. The organization has a dedicated LISTSERV with almost four hundred members and its website has received approximately thirty six hundred hits in the past year with a significant increase in the visits to the site last month (December 2013). NewSTEPs disseminates information and does training via webinars, as needed. Those webinars are available on the website. Fourteen webinars were held in the fall of 2013. Topics range from Memoranda of Understanding (MOU) to data repository training, education on CCHD and short term follow-up among other topics.

The data repository is goal three for NewSTEPs. Data in the repository include information on quality improvement and monitoring of changes in systems, disorder occurrence and practices, among other data. The voluntary data repository can be accessed via the main website. Components include state profiles with quality indicators. Information continues to be added here. Data elements in state profiles include demographics on babies born in the state, disorders screened, NBS policies, NBS program structure, IT and laboratory systems and HIT elements. Eight quality indicators established in the program have been developed by the community in a series of interviews, webinars and public comment periods. A quality indicator of interest of late is "Time elapsed from birth to screening, follow-up testing, confirmed diagnosis." There is variability across states in this indicator. Time elapsed is further broken down into eight components. Data on time from birth to specimen collection is collected for each state with the ability to look at the distribution across states and the national average. It is possible, therefore, to reach out to states that lag in order to help them improve.

The Case Definition Worksheets developed by HRSA are used by NewSTEPs contain twenty nine dried blood spot newborn screening conditions. These worksheets are available to NBS programs for data collection. Date of birth is not collected on these babies although there is a method to calculate the date, but no data event data are transferred to NewSTEPs. There are five categories in the diagnostic workup data collection form. Confidentiality is maintained.

Mr. Ojodu discussed the fourth goal of the organization which is "Technical Assistance." The organization is working on technical assistance and training opportunities for individuals in NBS programs in the areas of pre-analytic, analytic, post-analytic, short term follow-up and point of care.

NewSTEPs has created an evaluation tool to collect information from the states on their needs. The organization also does site visits upon request and produces a report following the site visit with recommendations on quality improvement issues. Questions can be submitted to newsteps@aphl.org

Discussion

- Dr. Parisi asked if the organization has considered partnering with other organizations that are part of the NBSTRN (Newborn Screening Translational Research Network), particularly around the data resource and longitudinal data resource issues and the R4S system (Laboratory Performance Database) to which states have been contributing data so as not to duplicate efforts. Dr. Sontag responded that NBSTRN collects data on long-term follow-up—point of diagnosis through the rest of life whereas NewSTEPs focuses on the short term to support the newborn screening program. However, there are many elements that could connect one system into the next system. They have talked to NBSTRN about having a global unique identifier that could be entered on the state level and then once the baby has consented to be in the longitudinal repository at NBSTRN we could link to that system for that baby. Conversely, states might get follow-up information, in return, on that baby from the longitudinal system.
- Ms. Bonhomme asked for more detail about the NextSTEPs' CCHD meeting scheduled for the end of February, 2014 as well as information on whether or not any public education will be provided as part of that meeting since the advocacy organizations were instrumental in states' adopting CCHD screening. Dr.

Sontag responded that the purpose of the CCHD meeting in February is to move all states forward—those that are already doing CCHD screening and might benefit from some quality improvements in their systems as well as those who are in the early stages of this testing. The target group for this meeting is the state NBS programs. Some representatives from advocacy groups might be welcome to attend the meeting. However, space is limited so that factor must also be considered for the February meeting.

- Dr. Watson clarified that NBSTRN does deal with long term follow-up as it relates to conditions that are part of newborn screening because some of those conditions are not well understood and we certainly need that data to understand clinical histories, etc. But from a research perspective, which is where the NIH's focus is, NBSTRN has interests across screening, diagnosis, follow-up—where new technologies, new methodologies, new conditions and pilots may come into play—because it's certainly going to cover—certainly in pilots—everything from screening to follow-up where everything comes together to make decisions about NBS.

V. Public Comments

Sarah Wilkerson, Board Member, Save Babies through Screening Foundation: Ms. Wilkerson is a mother of a MCAD child who passed away before the family learned of his condition. The state laboratory was closed in Colorado when her son was born and there was a delay in getting his newborn test results in a timely manner. There is a well established protocol for treating MCAD, but it could not be put in place given the delay in getting the test results. Colorado is not the only state with limited weekend laboratory hours. Twenty-seven states have limited weekend availability despite the fact that babies are born every day including weekends. Mrs. Wilkerson urged the DACHDNC to consider the issue of weekend hours for laboratories as they examine ways by which test results might be accelerated.

Response
Dr. Bocchini thanked Ms. Wilkerson for her comments and informed participants that as a result of her comments at the September meeting, the DACHDNC agreed to move forward in working with the APHL and the CDC to evaluate the timeliness of newborn screening; that process is underway. He assured her that her comments will be taken into consideration.

Kay Kelly, Parent of a child with MCADD: Ms. Kelly thanked the Committee for the opportunity to speak. Her newborn son was diagnosed with MCAD. Thanks to the rapid newborn screening they were given a procedure to save his life. They woke him up every two hours and fed him. They were lucky. All families need to receive information in a timely manner to save lives. Ms. Kelly is advocating for improved education for hospitals about the dangers of batching samples and mandated use of courier services to ensure that samples make it to laboratories in a timely, traceable manner even on weekends and holidays. Further, she would like to see assistance given to state laboratories to help them identify new technologies or resources that will allow them to process samples seven days a week.

Response
Dr. Bocchini thanked Ms. Kelly for sharing her story and illustrating how effective NBS can be when it is properly done.

Dr. Gerald Raymond, Director of Child Neurology and Professor, University of Minnesota: Dr. Raymond spoke in support of the nomination of X-linked Adrenoleukodystrophy (X-ALD) for inclusion in the RUSP. X-linked ALD is a genetic disorder caused by mutations in ABCD1 gene which affects peroxisomal beta oxidation. Patients accumulate high levels of very long chain fatty acids (VLCFA) in all tissues. It affects approximately one in seventeen thousand individuals and all ethnic groups. The primary manifestations in childhood are Addison's disease or primary adrenal insufficiency and cerebral disease. Addison's disease can occur in the first year of life and results in significant morbidity and mortality in affected boys. With identification, patients can be monitored for development of Addison's disease and treated. The other manifestation, cerebral disease, is a devastating event, but it, too, can be monitored for and detected by MRI and surveillance allows for referral for treatment with stem cell therapy. A method to detect the disorder using newborn blood spots has been developed and has been shown to be sensitive and specific for impaired peroxisomal beta-oxidation defects and several papers have been published on this topic. The most recent paper is on a pilot study in five thousand newborns in Maryland. Recently New York

State NBS Program added ALD to their screening panel. The system went live on December 31, 2013 and there have already been two referrals. Those individuals are being assessed and confirmed. Dr. Raymond hoped the Committee would look favorably upon the proposal today.

Dr. Amber Salzman, President, Stop ALD Foundation: Dr. Salzman wished to add further context to the updated ALD screening nomination. The DACHDNC reviewed the nomination to add ALD to NBS in September 2012 and asked for more data from the Mayo pilot study before moving forward. Data from that study are now included in the revised nomination. The study results further support the validity of the test. Patient advocates supported by ALD physicians and scientists have been working with several states to prepare to implement ALD screening. As mentioned by Dr. Raymond, this screening has already been implemented in New York State. There is a reliable approach to do biochemical screening of blood spots and processes are in place to do molecular screening of specimens that are positive upon biochemical screening and support exists in the communities for families whose babies are found to be positive. Early warning is the only way to ensure that children are treated in time for that treatment to be effective. Several hundred babies will be born in the U.S. with ALD this year. Dr. Salzman urged the Committee to move the nomination forward to the External Condition Review Group.

Response
Dr. Bocchini thanked Dr. Salzman for her comments. The additional information requested has been sent to the Nomination and Prioritization Workgroup. The results of their evaluation of that information will be presented to the Committee later during this meeting.

Dean Suhr, President, MLD Foundation: Mr. Suhr reported that the U.S. Senate is moving forward with the reauthorization of the Newborn Screening Saves Lives appropriation. The Congress has not yet approved this reauthorization. Mr. Suhr hopes to hold a summit in the fall of this year on the topic of the criteria needed to add a condition to the RUSP. Currently, a viable therapy must be in existence before a newborn screen can be added. Mr. Suhr acknowledged that there are various types of issues related to adding a condition to the RUSP without a viable therapy. However, he urged other advocates to join him in this effort. He can be contacted at Dean@MLDfoundation.org or via contact methods found on the MLD Foundation website.

VI. X-lined Adrenoleukodystrophy (ALD)—Update From Nomination and Prioritization Workgroup

Dietrich Matern, MD, PhD, FACMG
Professor of Laboratory Medicine, Medical Genetics and Pediatrics
Biochemical Genetics Laboratory
Mayo Clinic College of Medicine

Dr. Dietrich Matern spoke on behalf of the Nomination and Prioritization Workgroup summarizing their discussions of the nomination of X-ALD. Dr. Charles Peters is the primary proponent of this nomination supported by nine advocacy organizations. Dr. Matern provided some background on X-ALD and its prevalence. It is X-linked recessive with a prevalence of one in approximately twenty-one thousand males. Approximately sixty-five percent of carrier females develop the disease by age sixty. It is the most common peroxisomal disorder. It is caused by mutations in the ABCD1 gene which encodes peroxisomal membrane protein ALDP, a transmembrane transporter of VLCFA. The ALDP deficiency results in impaired VLCFA peroxisomal beta-oxidation which causes accumulation of VLCFA-CoA esters in cells leading to oxidative stress and oxidative damage to proteins, microglial activation and apoptosis. The phenotypes are complex: Adrenocortical insufficiency (Addison-only), cerebral demyelinating form of X-ALD (cerebral ALD), adrenomyeloneuropathy (AMN). Variants can occur within the same family and there is no correlation between the phenotype and the genotype.

The phenotype in cerebral X-ALD starts slowly and is often misdiagnosed as Attention Deficit Hyperactivity Disorder (ADHD). Symptoms are typically not seen before about the age of two. It is a progressive inflammatory demyelination process within the brain which leads to severe cognitive and neurologic disability, a vegetative state and death within two and one half years of diagnosis or onset of symptoms. The laboratory diagnosis is made based upon elevation of VLCFA in plasma which can be confirmed by molecular genetic analysis looking at the ABCD1

gene. This is of particular importance if looking for carrier females because fifteen percent of that group will have normal VLCFA. Family investigations can lead to early diagnosis and treatment.

Adrenomyeloneuropathy (AMN) is a non-inflammatory distal axonopathy, contrary to X-ALD. It involves mostly the long tracts of the spinal cord. The phenotype is a progressive spastic paraplegia which is often misdiagnosed as primary progressive MS or as hereditary spastic paraparesis. About twenty percent of males with AMN will later develop cerebral ALD. Diagnosis of AMN is confirmed in the laboratory by elevated VLCFA similar to the laboratory diagnosis for X-ALD.

For NBS, the question which arises is whether or not there is treatment that can be considered for the condition. Treatment options for X-ALD include hormone replacement, Lorenzo's oil and hematopoietic cell transplantation (HCT). Dr. Matern cited results from a study from the University of Minnesota group published in 2011[1] on the probability of survival in boys with cerebral ALD treated with HCT based on the Loes score and neurologic function at the time of HCT. The Loes score is based upon MRI patterns, radiological features of the brain. A lower Loes score denotes a better chance of survival. A neurologic function score (NFS) is ascertained at the time of HCT. An argument can be made for including X-ALD in NBS so the condition can be identified and treated early.

For population screening, it would be optimal to have an easily administered test for NBS. Dr. Raymond and colleagues looked at measuring lysophosphatidylcholines (LPC) and biomarkers in the blood using liquid chromatography-tandem mass spectrometry. Dr. Silvia Tortorelli at the Mayo Clinic and others at the Kennedy Krieger Institute have worked to improve this assay. The goal was to move away from a LC-MS/MS to a simpler FIA-MS/MS method. Liquid chromatography adds some complexity to the test and the goal in NBS is to have the simplest possible method. Dr. Tortorelli also reduced the instrument time of each sample from 3 to 1.5 minutes which doubles the throughput and reduces the amount of equipment needed in the laboratory to do the testing. Additionally, the researchers multiplexed testing for six LSDs such as Pompe and MPS1 that are either recommended or being considered for inclusion in the NBS panel.

In 2012 the Committee decided not to send the nomination to the External Condition Review Group since there was insufficient prospective data at that time from a large pilot study which was ongoing at the Mayo Biochemical Genetics Laboratory. Dr. Matern presented findings from that Mayo NBS study of up to thirteen LSDs, Wilson disease, Friedreich Ataxia and X-ALD. The study analyzed de-identified dried blood spots (DBS) obtained from the California NBS laboratory to identify an effective, efficient testing approach. Additional study objectives included ascertaining a rapid approach to confirm a presumptive diagnosis using biochemical and molecular genetic analyses and building a web site for data collection and analyses. Dr. Matern next presented study findings of flow injection analysis (FIA) of C24 and C26 which are helpful in picking up X-ALD. If the FIA was not normal, a second tier analysis was done. A reinjection of the prepared specimen was done using liquid chromatography to separate particularly C26. For C26 there is sometimes interference from the filter paper in some blood spots; it does not come from the patient, but that interference can cause false positive results. Therefore, the LC-MS/MS was used as a second tier test and if that was not normal it was presumed positive and follow-up was done. Fifty-one X-ALD positive patients were picked up in a retrospective analysis of samples from known patients and twenty-four carriers were identified. These were not all picked up from the one hundred thousand study participants; they were retrospectively analyzed to identify ranges and to figure out what works best. Molecular testing of the abnormal results of the last fifteen thousand samples has not been completed because funding ended in September 2013. Among the first eighty-five thousand samples tested, for X-ALD, approximately one percent had an elevation (640 females with an elevation and 274 males). In second tier testing only 25/640 females and 10/274 males had an abnormality and ABCD1 genotyping found X-ALD in one female carrier and 2 male X-ALD patients; other peroxisomal disorders are not excluded at this point since this genotyping was just for ABCD1.

Dr. Matern summarized the key points in his presentation as follows:

- X-ALD is a serious medical condition
- The natural history of X-ALD appears to be well known.
- X-ALD does not require initiation of treatment in the newborn period, which may be a concern since generally something is not added to NBS if treatment is not required immediately.

[1] Miller WP et al. Blood 2011, 118: 1971-8

- DBS-based assays are available for X-ALD using LPCs as a disease marker although LPCs are not specific for X-ALD; they are elevated in other peroxisomal disorders. Therefore they would represent secondary targets. LPCs will be elevated in female carriers although the testing will not identify all carriers.
- A pilot study of one hundred thousand de-identified samples is currently being completed at the Mayo Clinic. It is anticipated that the study will be completed by the end of February. That study used a two-tier approach, however not one including molecular testing. The second tier test could be done locally or at the regional level.
- The Mayo Clinic pilot study found a prevalence of X-ALD of one in twenty-one thousand two hundred fifty boys. The false positive result was 0.02% and the positive predictive value is eighteen percent. The false positive rate at the Mayo Clinic for AA/OA/FAO was .02% and the positive predictive value was 68% for those 40+ conditions that were screened with this test. The national average for the same screen (AA/OA/FAO) is 0.46% which is considered acceptable. The positive predictive value nationwide for AA/OA/FAO is 18% which is consistent with findings for X-ALD in the Mayo Clinic study; therefore, the test used in the study will work.

Recommendations

- The Nomination and Prioritization Workgroup believes it is time to initiate the External Evidence Review of X-ALD for NBS. The SACHDNC previously stated that X-ALD is an important condition to consider pending results of data from pilot studies. The Mayo Clinic pilot study suggests that an appropriate approach for NBS exists.
- The Workgroup recommends that NBS programs that already screen for X-ALD participate in the R4S Laboratory Performance Database and that the ACMG develop algorithms for X-ALD and relevant peroxisomal disorders that are also identified by the screen.

MOTION

Dr. McDonough moved to advance X-ALD for External Evidence Review. Dr. Lorey seconded the motion.

Discussion

- Dr. Botkin commented that it was not clear from the presentation what is known about the spectrum of the disorder. Different subtypes were mentioned. Dr. Matern responded that the spectrum of the disease is basically the cerebral onset form, AMN, and Addison's disease. He added that although he is not an expert on ALD he would expect that adding X-ALD to NBS would teach us more about the condition and would help elucidate whether there are other milder variants. But this is a slowly progressive condition meaning over several years. Most patients are symptomatic by the age of four years.
- Dr. Parisi asked about the lack of specificity for starting treatment in the newborn period. It appears that with Addison's disease it is important to start treatment so patients do not go into adrenal crisis. Therefore, it seems that it might be important to start treatment as early as possible. Her second question asked about those who screened positive after the second tier liquid chromatography step, but did not have an ABCD1 mutation and presumably some of those may have other peroxisomal disorders. Is follow-up being done on those cases or does anyone have a plan in place for them? Dr. Matern responded that in terms of those with Addison's disease only, based upon the literature, most patients do not present in the first years of life. It does not appear to be a neonatal condition. In terms of those cases with abnormal results in the screening, but without an ABCD1 mutation and no other molecular testing, the goal is to work up those cases completely and to look at other peroxisomal conditions by molecular means, but he does not have that data yet.
- Dr. McDonough commented that it is important to consider conditions that do not need treatment right at birth. Addison's disease often does not present until after age two, but it a sneaky condition and it is important that physicians taking care of those children and their families have a heads up about what's coming and what they can do to prevent problems.
- Dr. Botkin asked about prevalence of carrier status and whether anyone has made recommendations about management for females who may be carriers? These are females who may have manifestations many decades later and there may be reproductive implications for them, but is there anything to be done in the pediatric age group for female carriers? Dr. Bailey wished to ask the same question about female carriers. Dr. Matern replied that he is not aware of any recommendations for female carriers. The Dutch decided not to screen for carriers due to the much later onset of symptoms and still a good

number of carriers never have any symptoms. He added that based on the study he and his colleagues conducted the overall incidence is one carrier in eighty five thousand, but, again, they would not pick-up all of them so he assumes that there are more that they missed than they identified. Part of the evidence review would certainly include a review of the New York protocol that the Kennedy Krieger Institute and Dr. Raymond were instrumental in putting together. Dr. Bocchini commented that the question about female carriers is something the Condition Review Team would evaluate if the Committee decides to recommend moving forward with this nomination rather than trying to have the DACHDNC attempt to solve that issue.

VOTE

- The Committee voted unanimously to move ALD to the Condition Review Team.

Dr. Bocchini thanked Dr. Matern for his presentation, the Nomination and Prioritization Workgroup for their work and those who have been instrumental in working with the Committee to bring this nomination forward. The Condition Review Team will update the DACHDNC over the next few meetings on their progress in reviewing this nomination.

VII. Committee Business—January 17, 2014

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

Voting members present were: Dr. Bailey, Dr. Bocchini, Dr. Botkin, Dr. Dougherty (AHRQ), Dr. Homer, Dr. Kelm (FDA), Dr. Lorey, Dr. Lu (HRSA), Dr. McDonough, Dr. Matern, Dr. Parisi (NIH), Dr.Thompson, Ms.Wicklund, Ms. Williams, Ms. Sarkar (DFO).

Nonvoting organizational representatives present were:

- AAFP: Dr. Chen
- AAP: Dr. Tarini
- ACMG: Dr. Watson
- ACOG: Ms. Saraco
- AMCHP: Ms. Kate Taft
- APHL: Dr. Tanksley
- ASTHO: Dr. Kus
- DoD: Dr. Kanis
- GA: Ms. Bonhomme
- March of Dimes: Dr. McCabe
- NSGC: Ms. Vockley
- SIMD: Dr. Greene

VIII. Newborn Screening Specimen Transport—Update

A. Update from Laboratory Standards and Procedures Subcommittee—APHL Survey

Susan Tanksley, PhD
Manager, Laboratory Operations Unit
Texas Department of State Health Services
Austin, Texas

At the September 2013 meeting a parent reported that there had been a delayed diagnosis of a metabolic disorder in her child. The Committee decided to do a closer review to see if this were an isolated incident or if there were other issues related to timing of specimen transport. The Committee charged the Lab Subcommittee to work with them and to initiate a survey to evaluate timeliness of receipt of specimens across the states. Subsequently, a series of articles were published in the *Milwaukee Journal Sentinel* indicating that there were problems, at least in the reports from states that participated in a survey, in timely receipt of specimens and in turnaround time for data. The Subcommittee on Laboratory Standards and Procedures was asked to research issues related to the timely handling of samples and to provide feedback on whether or not the Committee ought to make recommendations regarding this issue. This task to the Subcommittee falls within Priority B: Provide guidance for state NBS Programs in making decisions about lab implementation, integration, follow-up (FU) and quality assurance (QA). The Subcommittee first gathered background information working with the CDC and APHL. The Subcommittee reviewed previous recommendations such as the 2005 ACMG report and CLSI guidelines. The Subcommittee may later also review the CAP newborn screening guidelines.

APHL conducted a Web-based survey of states. The survey was sent to State NBS laboratory directors, managers and follow-up coordinators to be completed December 19, 2013 to January 6, 2014. Thirty-two states have responded to date and responses from six other states are pending. QA and data control checks were performed on the data provided although some states could not provide the data in the manner requested. States responded to the question regarding method used to transport specimens from birthing hospitals to the NBS laboratory as follows: Courier services (18); Overnight delivery services (19); U.S. mail (20); Other (8). States could provide multiple responses to this question. Responses regarding policy/practice/recommendation/law on when specimens should be received by NBS programs from the hospitals found that: 62% had a policy/practice/recommendation/law on when specimens are received; 19% had no policy/practice, etc; 19% had a policy/practice, etc. governing when specimens should be sent from the healthcare facility to the laboratory. Among the twenty-four states that responded to the question on whether or not the state has regulatory authority to fine or sanction hospitals that do not comply with state laws for sending samples in the state-specified timeframe: 17% (about four states) have such regulatory authority. In terms of review of transit performance of hospitals by NBS programs: 31 NBS programs keep a record of transit performance by hospitals; 29 state NBS programs review transit performance times and 30 state NBS programs provide feedback to birthing hospitals on transit performance. Such feedback is given via the following: Report cards; Quality Improvement tools; educational materials; newsletters or direct communication either in-person or via telephone. In terms of laboratory operating hours: 12/32 State NBS programs indicated that their labs are consistently closed on Saturdays and Sundays; 20/32 respondents said their laboratories are open at least six days per week; 4/20 respondents indicated that laboratories only receive specimens and do not do any other activity on Saturday or Sunday. Six of the twelve labs that are currently closed on weekends are considering opening at least six days per week within the next one to two years. In terms of follow-up operating hours: 17/28 (61%) are consistently closed on Saturdays and Sundays; 11/28 (39%) are open at least six days per week; 20/31 (65%) offer after hours paging/on call services on Saturdays and Sundays.

Through the NewSTEPs Program several quality indicators have been proposed and will be included in their database. Indicator number 5 concerns "Time elapsed from birth to screening, follow-up testing, confirmed diagnosis. States will be requested to submit these data to the NewSTEPs database annually. All 32 survey respondents noted that the timeframe from birth to specimen collection was within 24 to 48 hours. Seventeen states answered the question on median time in days from specimen collection to receipt by the lab in the state. Six percent of respondents said the median time was less than one day; another six percent said the time was between one and two days; forty-one percent said the time was two to less than three days; forty seven percent said the median time was three days.

Dr. Tanksley outlined limitations of the survey which included the following: Short time allowed to respond to the survey and the fact that the survey was conducted during the Holidays; some data including the time quality indictor were incomplete; definitions of quality indicators could have been included in the survey for clarity; some questions might be open to interpretation. APHL is attempting to collect additional data on the survey and will follow-up with states. The survey goal is to get one hundred percent of the states to respond; as of this time, only 32/50 states have responded.

Dr. Tanksley next summarized information from Dr. Michael Watson's presentation on "ACMG Standards for NBS and Their Oversight." The ACMG evaluated scientific and medical information related to screening for specific

conditions and made recommendations based upon the evidence. Out of that work a report was published in 2006 (sometimes referred to as the "2005 Report"), "Newborn Screening: Toward a Uniform Screening Panel and System." Ten program standards were recommended in Section II of that report including the standard regarding improvement of turnaround time in reporting screen-negative results. All results at a minimum should be available less than five days after blood sampling. Most results should be available within two days of the specimen arriving in the lab. Finally, specimens should arrive in labs within three days of collection. However, if specimen transit time takes three days it is very difficult to get the results out within five days. Information in another section of the report states that specimens should arrive at the lab within twenty-four hours of collection.

Another program standard mentioned in the report concerns hospitals and (formerly) JCAHO (now The Joint Commission) and their roles. Hospitals must play a very active part in ensuring that specimens get to the laboratory, with accurate data submitted with the specimens, tracking those specimens and making sure that results are reported back in a timely manner and that if results need to be followed-up, the hospital must participate in that process. ACMG initiated conversations with JCAHO, now the Joint Commission in late 2003. Discussions included the following issues: The role of the hospital in transmitting samples to screening laboratories; the role of the hospital in contacting patients for follow-up; alignment of NBS standards with reporting priorities of the Joint Commission. It was determined that an analysis of established legal liabilities associated with NBS activities was needed. That analysis was completed in 2008. It may now be time to again engage with the Joint Commission on establishing standards for NBS for hospitals.

The six components important in a NBS system are: Education throughout the process starting in the pre-natal period and reaching everyone who is part of the newborn screening process; screening which includes specimen collection and testing; follow-up of any out-of-range results and reporting those results in a timely manner; diagnostic confirmation of NBS results; management of patients with NBS disorders throughout their lifetimes; and program evaluation and continuous quality improvement to try to improve all aspects of the NBS system. If each step in the NBS is considered to be a process, then each of those processes can be measured if you have an accurate means of data collection and the data can be queried for analysis. Phases of NBS include pre-analytic phase which starts with initial NBS specimen collection and its transit to and receipt in the lab; analytic phase when an abnormal DBS screen result is found; and the post-analytic phase which goes from the time of NBS physician notification, parent notification, confirmatory test collection, confirmatory test result to treatment intervention and through management of that patient. Timing of collection can be measured (24 to 48 hours); transit time from collection to receipt in the lab for testing; time to result or time to report from specimen collection to screen results or from birth to screen results or time of receipt in the time to reporting of result; time to treatment is probably the most important time point—from birth of the child to treatment of the disorder.

Page 80 in the 2005 Report refers to transport time and recommends use of courier services to allow receipt of the specimens at the labs within 24 hours, particularly since some conditions can be life-threatening. There should be a five day turnaround time between birth and receipt of the testing results, per the report. That recommendation is for time sensitive disorders and the definition is five days from birth to availability of testing results versus elsewhere in the report where the recommendation is five days from specimen collection to the result report..

Key points in the Subcommittee's discussion included the following:

- Sample quality is critical to timely results
- Access to data is important in order to be able to see outliers
- Education about the time-sensitive nature of NBS is needed throughout the healthcare system
- March of Dimes is convening a consortium to discuss issues related to timeliness in NBS
- Further review of the Appendix in the ACMG report is needed
- Iowa is an example of a good state system with testing and reporting seven days per week
- Best Practices should be compiled and shared
- Perhaps re-examine recommendations and their validity/need to update or add new ones

B. Proposal for DACHDNC Discussion and Potential Recommendations

Kellie Kelm, PhD
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

Dr. Kelm presented the Subcommittee's recommended points for the DACHDNC to consider.

- The first point is to re-affirm the recommendations in the 2005 report and to strongly urge that states work toward achieving the timeframes recommended in that report. As part of that effort data on timeliness and Best Practices should be collected working with stakeholders and others.
- Given that new technologies have arisen since 2005 and conditions have been added, a determination should be made regarding whether or not recommendations should be clarified or updated.
- To avoid duplication of efforts to address timeliness of NBS issues, attempt to coordinate independent efforts.

Discussion

- Dr. McDonough commended the work of the Subcommittee, parent advocates and the investigative journalism of the *Milwaukee Sentinel Journal* for raising awareness of this issue as well as the state of Iowa which reports results even on weekends. He commented that MCHB is looking at straw objectives in the block grant program and it is important that NBS have objectives. Timeliness of collection could be added to help MCH programs work with public health programs. It would be appropriate for the DACHDNC to make a recommendation for the Secretary to be sent out to the states on timeliness rather than simply endorsing the ACMG report from 2005.
- Dr. Homer agreed that stronger recommendations could be crafted. The 2005 criteria could be used as a floor for recommendations as we continuously strive to improve. Tracking outliers rather than the median is important. He asked if there is a national approval/accreditation process perhaps through APHL for state laboratories. If so, that might be a means by which improvements could be implemented, e.g. staffing, internal processes, number of hours the laboratory is open, etc. State Health Departments regulate as well as cooperate with hospitals currently so that relationship should not affect efforts going forward to improve timeliness. However, Dr. Tanksley responded that NBS is a State activity and therefore, other than the regulations from CAP or CLIA there is no regulatory enforcement unless it is at the state level. The NewSTEPs Program does have an Evaluation Team and states can request such evaluation of the NBS system within the state. Recommendations are made based on that evaluation and the evaluation is helpful for the state to use to make improvements in NBS. This is an external review by a non-regulatory authority which is helpful for the state to obtain needed resources to make improvements.
- Dr. Botkin wondered if data exist associating lab hours and reporting time. He also asked who pays for courier services. Dr. Tanksley responded that generally there is an association between lab hours and reporting time. Data were presented earlier on percentage of states with labs that were open or closed as well as data on percentages of states that had follow-up available or not available on weekends. In some states the laboratories report the results out themselves while in other states the laboratories use follow-up staff to report out the results. Although data are not currently available tying those two things together, a future survey could gather data on that specific question. In general, if a lab is testing and getting results on a Saturday, if there are critical results, they are being reported out. The less time-sensitive result may not be being reported out. Per Dr. Tanksley's experience in Texas, the lab is open on Saturdays and critical results are reported out on Saturdays. The lab has a list of prioritized disorders that are reported out on Saturday. The less time-sensitive conditions are reported out on Monday. With regard to courier costs, those costs were noted on a slide presented. In some states, the submitter, i.e. the hospital, pays the courier costs. In other states, the courier cost is included in the NBS fee and it may also be paid by the state itself or by the NBS program itself; it is probably a mixed model in some of those states.
- Ms. Wicklund asked if the survey had open text boxes to get a better idea from the state's perspective about the rationale behind the laboratory's hours as well as information about the barriers that exist to extending hours or opening additional days. Dr. Tanksley responded that the survey did contain some open text boxes for some questions. There was a question about barriers in the survey with multiple choice answers followed by an "Other" with an open text box. Some of the barriers include staffing and funding.
- Dr. Parisi asked about the proposal to re-affirm the 2005 Report noting that at least one discrepancy in that Report has already been discussed (i.e. recommended timeframe between collection of the specimen and

receipt in the lab, i.e. 24 hours in one place and 3 days in another place in that Report). Therefore, before we recommend that the 2005 Report be re-affirmed it might be worth clarifying which recommendations we are re-affirming. Additionally, number two on the slide (give consideration to new technologies and conditions added since 2005 to determine whether recommendations need to be updated or clarified) ought to come before number 1 (re-affirm recommendations in the 2005 Report). Dr. Parisi also asked if there has been any discussion of lag period of transport given temperature fluctuations either in very cold climates or in very hot climates during certain times of the year and how that might degrade specimen integrity as a factor in the reliability of sample collection and testing. Dr. Tanksley responded that temperature fluctuations and lag time and how those might impact specimen integrity were not part of the discussion. The Subcommittee had limited time and would like to further discuss these points. In hot climates specimen degradation is an issue, speaking from experience in Texas. A Courier Pilot Study in Texas found a decrease in the incidence of false positives for galactosemia because specimens did not have enzyme degradation from the heat.

- Dr. Kelm added that the Subcommittee would agree that it would probably be valuable to reassess the goals in the 2005 Report; however, the Subcommittee thought most of the goals in that Report were still valid goals that NBS systems should be meeting right now. Perhaps we ought to specify which of those recommendations the NBS system should meet right now.
- Dr. Matern agreed that the verbiage might not be consistent in the ACMG Report. However, the DACHDNC could endorse the recommended timeframes shown in Dr. Tanksley's presentation, i.e.
    - Transit Time: receive at lab within 24 hours of collection;
    - Time to result for critical results should be within 5 days of life;
    - Time to result for all results should be within 5 days of collection
- Dr. Tanksley asked to read from the 2005 Report from the sections on transit time of 24 hours versus 3 days to provide more background. Page 80 talks about a survey that was done and how specimens were sent to the laboratories at that time. It is suggested that specimens be transported by courier services that allow for receipt at the testing laboratories within 24 hours. Then on page 93 of the report which is where the ten recommendations are found, as part of recommendation number 4 on turnaround time, the last statement of that recommendation says that most results should be available within two days of the specimen arriving in the laboratory and specimens should arrive in the laboratories within 3 days of collection.
- Dr. McCabe provided some information about the consortium with the March of Dimes as the convener. To date only a single, one-hour conference call has been held with six of the currently participating ten organizations. Timeliness is not the only issue being considered. The March of Dimes proposed an approach which appeared in their op-ed piece in the *Milwaukee Journal Sentinel*(MJS) on November 23, 2013 entitled, "Baby Tests Require a Culture of Safety." They argued that the system is complex with many vulnerabilities. We are trying to prospectively identify multiple vulnerabilities utilizing the High Reliability Organization (HRO) paradigm which is used in hospitals for safety. This came out of the nuclear energy and aviation industries. Therefore, what was brought to our attention as a time-sensitivity issue from the *Milwaukee Journal Sentinel* (MJS) could offer an opportunity to look at many issues beyond just timeliness which are inherent in any complex system. Dr. Homer reinforced Dr. McCabe's suggestion to use the HRO framework bringing that element of safety science into the work.
- Ms. Bonhomme commented that while we know there are standards in place and suggestions about which we, in the NBS community, are aware those doing the NBS may be unaware of these standards related to the practicalities of collecting, handling and transporting specimens, etc. A key piece of "Baby's First Test," is educating healthcare professionals. We have done a lot of work with nurses in the nurseries to get them to understand and to do proper training on timeliness of collecting specimens and getting them to the laboratory. As we think about recommendations and strategies for improvement we should look at projects that have been funded and carried out whether those projects were on a smaller or on a larger scale to understand what has worked and how we might proceed. This is not just a laboratory issue, it is an educational issue and we need to understand how to educate the ones who have the control to put the specimen in the mail or not. These are important considerations as we develop strategies moving forward.
- Dr. Greene emphasized the importance of JCAHO/The Joint Commission. Education is very important. The MMWR Good Laboratory Practices for biochemical genetic testing whether in a biochemical lab or in a NBS lab contain a Continuing Education (CE) activity. If The Joint Commission has a marker for hospitals then there will be education and there will be compliance. Otherwise, it's incredibly important to

the families, but it's not high on the priority for the busy nursery or for the laboratory to educate all the new people who come into the system. The Joint Commission should be encouraged to make this a sentinel event.

- Participants continued to discuss what guidance the Committee might offer to the Subcommittee at this point, particularly with regard to the transit timelines. Dr. Matern asked if the Committee will request that the Subcommittee consider the transit times in the 2005 Report the minimum standard right now although for CCHD and the point of care items there might be differences. Dr. Greene agreed with Dr. Matern's comment and wondered if it would be appropriate since the 2005 recommendations are not specific to any particular tests. However, Dr. McDonough wondered about responding to the current problem by reaffirming what is in a nine year old report. If the Committee goes forward it might be wise to set a timeframe within which a statement would be developed. The interim step would be to send something out to the State Health Departments or to the Public Health Labs. Dr. Bocchini understood Dr. McDonough's concern, but explained that the plan is to put the Committee on record while the Subcommittee continues to come forward with more specific recommendations, guidance, working potentially with the Joint Commission and addressing other issues which the Subcommittee and members of the full Committee have brought forth today.
- Dr. Greene commented that while she would like to see a stronger statement, given simple geography and constraints on time, she does not think it would be possible to get samples to the lab before 24 hours of collection. The discrepancy in the 2005 Report probably reflects the difference between the ideal mentioned in the body of the Report versus what is achievable which is found in the final recommendations.

Next Steps for the Laboratory Standards and Procedures Subcommittee:

- Dr. Matern supported using what is on the slide regarding timelines (discussed above) as a baseline of what should be done right now, particularly transit time from birth place to screening lab. Dr. Bocchini said the Committee will go forward with that. Part of the reassessment by the Subcommittee is to determine, based upon the number of things being evaluated, what moves into the critical result category versus those that can be reported within 5 days of collection. That would separate out the hearing and other things that are not critical tests.
- The Subcommittee is asked to look at reassessment and to meet in-between full Committee meetings and to bring forth a proposal to be reviewed by the full Committee by email. Once that has been finalized we can compose a strong statement that the Secretary can remind the states that this is a recommendation of the Committee.
- The Subcommittee would be asked to work on the issues it has identified and to further analyze the survey and develop some Best Practices and determine other organizations with which we might collaborate. Related to that point, the Subcommittee could address the issue of engagement with The Joint Commission and with the American College of Medical Genetics. With the prior work of the ACMG this might be a good opportunity for us together to approach The Joint Commission to determine whether they would make timeliness of NBS from the hospital side a core measure for hospitals.
- The Subcommittee should also be tasked with considering:
  - Accountability from the hospital side for obtaining and processing specimens appropriately to meet the timeline
  - Look at transparency and determine whether the Committee could provide guidelines to the states or recommendations on how to address specific hospitals in attempting to address the outliers. We now have a snapshot with median times but we need a way within the states to recommend that outliers can be identified so they can be addressed appropriately within the states.
- The Subcommittee is asked to make the first bullet point in the information on timelines (shown on the slide discussed previously) a reaffirmation of collection time within 24 to 48 hours. That is the current standard, but there was agreement that it to be included in the bullets.

IX. Mucopolysaccharidosis Type 1 (MPS-1)—Update From Condition Review Team

Alex Kemper, MD, MPH, MS

Condition Review Workgroup
Associate Professor
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Dr. Bocchini introduced Dr. Kemper and provided information on Dr. Kemper's background and experience. He then turned the meeting over to Dr. Kemper who provided a high level overview of MPS-1 and acknowledged the members of the Condition Review Workgroup. Drs. Botkin and McDonnough serve as liaisons from that Workgroup to the DACHDNC and have provided valuable input on how to summarize very complex material.

MPS1 is an autosomal recessive Lysosomal Storage Disorder (LSD) caused by deficiency of α-L-iduronidase (IDUA) enzyme. It is a progressive, multi-system disorder with variable clinical symptoms. There is a continuum of disease severity and there are different ways to divide the severity. The two general divisions are severe (Hurler syndrome (H) and attenuated form includes Hurler-Scheie syndrome (H/S) and Scheie syndrome (S). These MPS 1 conditions are heterogeneous and overlapping. The overall estimated incidence is approximately one case per one hundred thousand. The severe form, Hurler syndrome, is the predominate type although clinical epidemiology studies are at risk for bias for under ascertainment. Some subgroups have a higher incidence, e.g. traveler population in Ireland has a higher incidence.

Onset in Hurler starts at 1 year and is rapidly progressive while in Hurler/Scheie onset is by age 3 to 4 years and in Scheie onset is variable—at 2 to 12 years and has less progressive problems. Cardio-respiratory failure is seen in Hurler's, cardiovascular disease in Hurler/Scheie and valvular heart disease in Scheie. In the Hurler form severe respiratory problems are seen including obstructive airway disease with similar symptoms in Hurler/Scheie and upper respiratory infections in Scheie. Those with Hurler if untreated die before age 10; those with Hurler/Scheie die in the teens or 20s; those with Scheie death is later in life- most have a normal life span. These are heterogeneous groupings, however, so those with Hurler/Scheie may have a lower life expectancy. Data from the MPS 1 Registry from its beginning in 2003 through March 2010 with patients from 33 countries do not have a disease classification for each patient entered. Registries may not provide a good sense of the overall distribution of the condition. However, age of onset, diagnosis and treatment initiation time in age and median age of death are documented in the registry data. Median age of death in Hurler is about 4 years of age while it is 17.4 years in Hurler-Scheie and 29 in Scheie although only 4 patients with Scheie are included so those data may be a little less reliable. In Hurler the median age at onset in registry data is around 6 months with treatment initiation around a little less than one and a half years of age. In Hurler-Scheie age at onset is closer to 2 years with diagnosis closer to 4 years of age and treatment initiation around 8.6 years of age. There are caveats associated with registry data, however, and the data reflect generally more severe cases.

NBS in MPS 1 is based on detection of low IDUA enzyme activity. It can be detected in DBS and like Pompe disease several screening methods can be used to detect the condition including tandem mass spectrometry (MS/MS), fluorometry by digital microfluidics and fluorometry on microtiter plate. Definitive MPS 1 diagnosis is based primarily on IDUA enzyme activity assay measured in leukocytes or skin fibroblasts although it only needs to be demonstrated in one place; it is not usually necessary to also get fibroblasts. IDUA activity less than 1% of normal is considered to establish MPS 1 diagnosis. Generally, IDUA activity does not predict the form or severity of the disease. Other things to support the diagnosis include measurement of increased glycosaminoglycan (GAG) levels in urine and genotyping is helpful if it reveals a known mutation; however, work is ongoing to discern the genotype/phenotype relationships in MPS 1. There are over 100 known MPS 1-specific IDUA mutations, but the challenge is that there are many mutations which are unique to specific individuals making predicting genotype/phenotype correlation more difficult. There is a known IDUA-pseudodeficiency mutation. Pseudodeficiency mutations have been previously discussed with relation to Pompe disease.

Several treatment strategies exist for MPS 1. Hematopoietic stem cell transplantation (HSCT) allows the individual to produce his own endogenous enzyme which is an advantage. Consensus Treatment Guidelines have been produced which suggest giving a transplant before age 2 or before age 2.5 years of age before much damage has been incurred. Patients should have normal to moderate cognition. One of the main differences between HSCT and enzyme replacement therapy (ERT) is that the enzyme replacement does not cross the blood-brain barrier (intrathecal administration has been proposed, but Dr. Kemper informed participants that he does not have data on

that treatment). For individuals with the more severe form of the disease, this is a way for the enzyme to get around the central nervous system. The second treatment strategy is HSCT with ERT. ERT has been reported in some small studies as a bridge prior to HSCT and it may augment enzyme activity after HSCT. There is some thought that ERT alone may benefit patients with all forms of the disease, but it is generally given to patients with the attenuated form.

The Condition Review looked at the net impact of NBS/early detection of MPS 1 relative to usual diagnostic and treatment practices on patient disease course and prognosis, population health outcomes and public health system impact. Components of patient disease course and prognosis include age of diagnosis, treatment initiation and outcomes and prognosis and survival. APHL has overseen the work on the public health system impact component. A systematic evidence review of MPS 1 screening and treatment effects relative to NBS for MPS 1 is being done. A decision analysis on population health outcomes of MPS 1 NBS is being overseen by Lisa Prosser at the University of Michigan. To understand the public health system impact of NBS for MPS 1 an assessment of the feasibility and readiness of the public health system to expand screening and follow-up of MPS 1 is being done. Expert Panel Members who assisted with the systematic evidence review included Barbara Burton, MD, Lorne Clarke, MD, Patricia Dickson, MD, Joseph Muenzer, MD, PhD and Barbara Wedehase, MSW, CGS. Their help is greatly appreciated. They will continue to assist particularly with unpublished data.

The systematic evidence review of published literature resulted in 194 studies to be retained for data extraction out of 2, 041 published articles. That number may decrease after final eligibility determination has been completed due to issues of overlapping case reports and fine tuning relative to meeting eligibility criteria. Among the states, New Jersey and New Mexico have began planning to include MPS 1 in NBS. Illinois evaluated digital microfluidics for screening for MPS 1about three years ago and the state is now in the preliminary phase of implementation to use MS/MS with a population pilot to be conducted starting this year. Missouri began a full population pilot testing LSDs with digital microfluidics platform in January 15, 2013 and continuing to the present time. They screen all newborns and follow-up with those who test positive. This is still considered to be a pilot study because they are fine tuning the meaning of a positive screen and the result is not being reported with all the other things included in a newborn screening. The MPS 1 NBS algorithm uses an IDUA assay (MS/MS fluorometric methods); internal laboratory cutoffs are used for IDUA low or within normal limits and to determine when to retest; if the IDUA continues to be low then the individual is given a diagnostic referral for testing of IDUA in leukocytes and fibroblasts and testing of urine GAGs and finally genotyping. If all that continues to be low the individual is sent to see a physician in a referral center. In this screening pilot about 84, 000 individuals have been screened between from January to December 2013 and the pilot is ongoing. Forty-two of those 84,000 have been positive: One MPS 1 case confirmed as severe MPS 1 (Hurler); two cases of low IDUA activity associated with genotypes of unknown significance; one carrier; five pseudodeficiency; sixteen false positives and seventeen pending status confirmation. These data are from personal communication and not to be distributed without permission from the Missouri DHHS NBS Program.

Dr. Kemper referred to one study of anonymous DBS in the state of Washington (Scott et al, 2013) and two population based Pilot NBS studies—one in Italy (Paciotti et al, 2012) and one in Taiwan (Lin et al, 2013). A study of anonymous DBS is not the same as conducting a population-based pilot study, but seeing the numbers can be helpful. Data from those three studies and from the Missouri Pilot Study show. The University of Washington study using genotyping and low enzyme activity found three cases consistent with MPS 1 but with no clinical correlation. The Taiwan NBS Pilot Study found two cases consistent with MPS 1 and a prevalence of 1 in 17, 643. The NBS Pilot Study in Italy found no cases among 3,403 newborns screened.

Dr. Kemper summarized current knowledge of MPS 1 NBS. It is known that IDUA activity can be measured although the screening algorithm is still being refined to balance case detection versus issues such as false positives and pseudodeficiencies. Challenges exist in predicting the form of MPS 1 or the severity.

HSCT compared to historical controls can lead to increased survival (less than 5% vs. 65% at 10 years; most HSCT mortality occurs within the first year after transplant probably related to risks associated with stem cell transplant generally). HSCT can lead to preserved development and improvement in mobility. There is little evidence on benefits or harms of HSCT in asymptomatic infants. It appears that earlier treatment is probably better although the ideal timing is not clear. Previous Expert Panels have recommended doing HSCT before 2 or 2.5 years of age. There is little evidence about HSCT + ERT; the treatment is more a matter of protocol.

Data on ERT treatment for attenuated MPS 1 from a randomized trial with six month follow-up show that such treatment can lead to improved outcomes in a six minute walk test and in the Disability Index. The benefit of ERT in asymptomatic cases of attenuated MPS 1 is not clear which is reminiscent of the conversations in the Committee regarding Pompe disease. In terms of the harms due to ERT treatment in attenuated MPS 1, with ERT there is a need for chronic infusions and risk of developing antibodies.

Next Steps for the Condition Review Workgroup

- The Workgroup will complete a systematic evidence review. The Workgroup has identified specialists who will be contacted for additional information.
- Modeling will be done to try to estimate the number of newborns expected to screen positive and be diagnosed with MPS 1, stratified by form and severity vs. uncertainty about what the form or the severity will be; we will compare that to expected outcomes from screening compared to clinical case detection.
- APHL is working on the assessment of the impact on the public health system. They will develop and administer a Stage 1 Web-based survey or surveys of the feasibility and readiness for MPS 1 in NBS in all the states and the District of Colombia. APHL will also conduct follow-up, in-depth interviews with select state NBS programs. They will then summarize the NBS feasibility and readiness data and complete that work at the time the full systematic evidence review is completed in order to allow the DACHDNC time to make a recommendation.

Questions may be directed to Dr. Kemper at alex.kemper@duke.edu

Discussion

- Dr. McDonough asked if we will be better off giving some time to allow the state of Missouri to collect more information from their Pilot Study. Dr.Kemper replied that more information is certainly always better. Missouri has been very forthcoming in sharing their information and more information would be helpful, but in terms of the timing I defer to all of you. Dr. Bocchini commented that when we reach that point we will ascertain whether there is enough data to make a decision. That will be an important component as it is for each decision about a condition.
- Dr. Homer wondered about the advantage of early treatment. It appeared that there was a significant lag time between onset of symptoms and time of diagnosis and then initiation of treatment. Is there any hint in the data or is that something you will need to model? Dr. Kemper replied that we can only model things for which we have some evidence. There are very small case series that suggest early identification and treatment is better. Those on the Technical Expert Panel felt very strongly that early identification would be important even if it did not lead to earlier HSCT but perhaps use of ERT while things were being sorted out and some musculoskeletal effects associated with MPS 1 could be minimized. But this is always the trap in NBS—until you start screening to identify those individuals it is hard to know the benefit of early screening. Dr. Kemper plans to follow-up with the Technical Experts and with those working on the Pilot Study in Missouri to better understand the benefits of early identification.
- Dr. Parisi commented that the dilemma of trying to predict the severity or phenotype on the basis of early detection by newborn screening is one we have seen before, but she asked if there were any correlation between or with residual enzyme activity and the likelihood of a more severe phenotype. As a corollary to Dr. Parisi commented that changes can be seen on MRI scan in patients with MPS 1. She asked if any of the protocols that follow these children longitudinally incorporate MRI or if there is an early enough marker that might predict CNS involvement and the need for sooner transplantation? Dr. Kemper responded that neuro-imaging is used once these children are detected and it should help figure out when to begin therapy or help in determining more severe versus the attenuated form of the disease. In a newborn, though, cognitive testing will not be that helpful. But that is a question we will ask the Technical Experts. The literature does not contain information on neuro-imaging use to predict severity or when to start HSCT. The issue of residual enzyme activity is key. If there is near-absent enzyme activity then the individual will have the severe form. But there is a gray zone where individuals have reduced enzyme activity, but it is not possible to predict the form of the disease. Some of the ongoing, not-yet-published work might help sort out this question. Some teams of researchers are going back and genotyping known cases of MPS 1. Currently we do not have the ability to use genotype to predict the severity or onset of the condition; that is

something that might change. The issues of residual enzyme activity, neuro-imaging and genotyping are going to be the keys to sorting out prediction and when treatment should occur.

- Dr. Matern commented that the study which he and his colleagues have been doing where MPS1 is included shows similar results in terms of the performance of the assays. They tested three different assays. However, there appears to be quite a difference between the published data and the data from Missouri in the number of cases identified. Dr. Matern added that in the study he and his colleagues are doing they have found approximately 1 in 4,000 who have a genotype that they cannot designate as pseudo-deficient. They are trying to figure out if these cases belong to a specific ethnic group in California. So the incidence of MPS 1 may be very underestimated now. He does not know what kind of phenotypes these cases are because most of them are variants of uncertain significance. We cannot follow-up these cases because they do not know who the individuals are. Dr. Kemper added that he and his colleagues will follow-up with Dr. Matern in a separate interview as they did previously.
- Dr. Greene wanted to reinforce what had been said about problems with genotype/phenotype. She appreciated Dr. Kemper's comments about ongoing research. Some of the mutations are of uncertain significance. The pseudo-deficiency genotype can be incredibly helpful. However, both for percent enzyme activity and for genotype there will be many people for whom we cannot predict severity. For Hurler's Syndrome unlike some of the other LSDs there are specific findings on physical exam and on x-ray. and Dr. Greene is not aware of that we would ever see neurologic problems before there are physical findings. That would be helpful in following up newborn screening; if you know what you are looking for it is there to be seen. The other question which may be helpful—we would like to have evidence from double-blind controlled studies about earlier intervention to see if it makes a difference, but the important point for MPS 1 is the course of the disorder causes progressive deformation of the joints, progressive heart problems, progressive problems with breathing and all of the symptoms of the disease then cause secondary problems. So it is very clear that if you can intervene before somebody has obstructive airway problems, the person won't get cardiovascular problems. Once a person has joint problems, once the joints are out of alignment and the cartilage is damaged, even if you improve the status of the joints, arthritis progresses because of the abnormal joint anatomy. So there is a physiologic reason why earlier treatment is better.
- Dr. Botkin commented that he is looking at the Missouri NBS Pilot information. There were 42 positive first screens. He asked for clarification about what constitutes the first screen. Does that mean analysis of the first blood spot? The protocol indicated that it is usually a retesting of the original sample that is part of that analysis. Dr. Kemper clarified that there is an in-house positive threshold that leads to retesting and if it is persistently below a threshold that they have sent then it is reported out as positive. These 42 positive that are listed are not just the first threshold, but these are ones that have been considered to be positive and these are the babies that have gone on to some sort of diagnostic follow-up. Dr. Botkin then asked about the 17 pending status confirmation and if there has been any additional follow-up on that group. That seems like a high number to be left in an uncertain stage. Dr. Kemper responded that these are numbers that Missouri shared right before the Holidays. There are approximately four or five centers that evaluate these individuals. It is unknown how long that process takes.
- Ms. Vockley commented that from a genetic counseling perspective, the laboratory potential for errors was mentioned and APHL is doing the public health system impact analysis. Are there plans to talk to people in the Missouri program about the experiences of these people, the 42 who are going through this extensive testing in order to get some insights on the repercussions of instituting MPS 1 in NBS? Dr. Kemper replied that, again, he would like to thank those in the Missouri program; they have been very forthcoming. The problem is in terms of understanding the benefits and harms of testing it is hard for us to evaluate those downstream since we cannot talk to those people directly. So we are limited in what we can say about false positives.

Clarification

- Dr. Kemper clarified that although we have reports that say New Jersey plans to add MPS1 to NBS, their law currently does not mandate that and they are now focusing on Krabbe, Pompe, Gaucher and Niemann-Pick and Fabry diseases. Then they will consider whether or not to add MPS 1.

Follow-up Item

- Ms. Vockley will follow-up with Dr. Kemper regarding the systematic review by some genetic counselors of the benefits and harms of genetic testing from the standpoint of the people who go through the genetic

testing process. Ms. Vockley will communicate with Dr. Kemper and give him more information on a potential publication and provide the name of a person to contact.

X. Subcommittee Reports

A. Subcommittee on Education and Training

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The Subcommittee is reviewing three conditions which may not be candidates for NBS but could benefit from earlier detection. Dr. Sihoun Hahn presented on "Wilson's Disease—Issues and Considerations for Childhood Screening." The Subcommittee then discussed nomination guidance, available materials and next steps.

In early childhood condition analysis, the Subcommittee decided that since the DACHDNC works on heritable diseases in newborns and children, it would be appropriate to think about childhood screening at a time other than the newborn period. We have been studying three diseases and looking at the following questions:

- What is the typical pattern of identification of children with this condition?
- What problems exist with the current pattern of identification- problems that could be ameliorated to some extent by earlier identification?
- Would population screening outside of the newborn period be at all feasible or desirable?
- In the absence of population screening, what could be the likely best case scenario for earlier identification?
- What level of effort would be required to substantially change the current paradigm—minimal, moderate, substantial or heroic?
- Which stakeholder groups would need to be engaged in any discussions about altering current practice?

Three conditions have been discussed: Fragile X Syndrome led by Dr. Bailey; Long QT led by Dr. Tarini; and Wilson's Disease led by Dr. Hahn. Typical pattern of identification of children with each of these conditions is being collected and will be presented at the next meeting. Information on each condition will be presented such as the definition, how common the condition is, consequences of the condition, etc. Patterns of identification for children with the condition will be presented and compared as well as information on problems that exist for children in each condition, for example, with Fragile X there are many problems with diagnosis and missing intervention programs; Long QT the first presentation could be unexplained sudden death; Wilson's Disease liver damage and other serious conditions could occur given the current pattern of identification. More detail will be discussed at the next meeting regarding the question about whether population screening outside the newborn period is feasible or desirable. The fundamental questions underlying that broader one about population screening is how and when and who would do it? Would there be stand alone screenings or would they be folded into a bigger panel and when would that panel occur? The Subcommittee probably will not have answers to these questions but these three conditions are very informative in helping us think through what the considerations might be.

The next question is in the absence of population based screening what is the next best scenario? In Fragile X, for example, if every pediatrician follows the guidelines for developmental screening at 9, 18 and 30 months and any child with a questionable screening is immediately followed by complete evaluation and any child with documented delay is immediately referred for genetic testing--even if all that is done, in the absence of population screening this would probably be symptom screening at 16 to 18 months diagnosis for most severely affected males. This type of

analysis will be provided for each of the three conditions. A related question to address is whether we always rely upon symptom screening and how to improve the diagnostic process once symptoms occur or should we do some symptomatic screening and if so, when should that occur. It would take much effort to change the current practice. Pediatricians and other experts would need to be involved.

The Subcommittee will finalize tables over the next few months comparing the three conditions, summarize major issues and themes that have emerged from this work and prepare a final report to be presented to the Committee in May. We do not anticipate any formal action items or requests to the Secretary to change current practice; this is intended as an exercise for informing the Committee to start thinking about things other than newborn screening.

Priority C: Provide better guidance for advocacy groups and others regarding the nomination and review process

Dr. Bailey next talked about the Subcommittee's work in keeping with Priority C. To address the problems in this area, the Subcommittee will work to increase public transparency for what the Committee does and provide rationale for decisions made.

Dr. Bailey described the current status with regard to activities designed in accordance with Priority C and proposed next steps. There is a description of the nomination process on the website now as well as the Nomination Form and the article by Kemper et al on the decision matrix and the decision-making process. A "Navigator" is needed to respond to questions and to provide guidance to nominators. Additionally, hyperlinks should be added to the Nomination Form to explain terms and to provide additional details about what is needed. The question is who will serve in the "Navigator" role. The Subcommittee will work with HRSA to answer this question. The Genetic Alliance has served in that capacity in the past. We will see if they may be willing to continue to do that if that is part of their agreement with HRSA. We also need to decide who will write some of the explanations and information to be linked to the Nomination Form.

B. Subcommittee on Follow-up and Treatment

Carol Greene, MD
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The Subcommittee's charge as revised in September 2011 is to engage in a multi-step process that

- Identifies barriers to post screening implementation and short and long-term follow-up including treatment, relevant to newborn screening results;
- Develops recommendations for overcoming identified barriers in order to improve implementation and short-and long-term follow-up including treatment, relevant to newborn screening results;
- Offers guidance on responsibility for post-screening implementation and short-and long-term follow-up including treatment, relevant to newborn screening results

Priority 1: Screening program implementation
As part of PriorityA the Subcommittee has been working on a project assessing challenges of new Point of Care tests. The case study is, "Some Lessons Learned from Early Hearing Detection and Intervention (EHDI) That May Be Applicable to Critical Congenital Heart Disease (CCHD) Screening." Dr. Kus presented information on this project. The major lessons in the paper are:

- State EHDI and NBS programs should strive to better integrate their various components.

- The State Health Department should play a leadership role in implementing electronic data systems that utilize standards-based messaging to reduce errors and enhance timeliness in data reporting.
- Screening programs should require child level data for quality improvement efforts.
- Appropriate financial support (federal and state) will be needed to develop, implement and maintain the CCHD screening system.

The Subcommittee is seeking acceptance from the Committee to go forward and publish this report.

Discussion

- Dr. Matern asked if the Subcommittee considered State rules/regulations/laws with respect to data privacy, data retention, including NBS results? In Minnesota, NBS results are being destroyed and the only record that is left is the medical record. Information in the paper is not entirely clear about whether the databases mentioned would have problems given some states' laws? Dr. Kus responded that particulars about state laws were not considered, but he and his colleagues are now trying to give general recommendations that we think would be helpful within the considerations of the states.

Next Step:

- Dr. Bocchini commented that since this was brought to the full Committee and they had opportunities to provide input and Dr. Kus has delineated the four major lessons in the paper, after today's feedback the paper ought to go forward because the Committee has already approved the changes that were recommended then and any changes recommended now can simply be added to the paper. This can go forward as a publication of the Committee. The publication will be posted on the Committee website when it is published.

Priority 2: Real world impacts and outcomes

As part of this Priority the Subcommittee previously submitted a draft of a paper tentatively titled, "A Framework for Assessing Outcomes from Newborn Screening: Do We Know If We Are Achieving The Promise of NBS?" Several new drafts have been developed. The Subcommittee is now rewriting and considering whether or not this ought to be divided into two papers and testing this framework which was developed using Sickle Cell and now we are testing it against PKU. We have had several discussions since our last presentation to the Committee making sure we addresses issues such as privacy and the family point of view, use of and study of use of EHR and avoid duplication among other issues. The work is definitely still in progress. We hope to have a draft to submit to the Committee for approval before May.

C. Subcommittee on Laboratory Standards and Procedures

Kellie Kelm, PhD
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Division of Chemistry and Toxicology Devices
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Silver Spring, MD

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Dr. Kelm reported that most of the Subcommittee's time has been spent on issues related to the timeliness of transport. However, the Subcommittee did briefly discuss one other item.

SUAC Implementation Project Update

Dr. Kelm pointed out that tyrosine is not a specific marker for TYR 1, but is also elevated in other conditions. Succinylacetone is a specific marker for TYR 1, but it is not detectable by routine NBS. It can be detected by mass spec. It is available in one commercial kit, but not in another that is available and used by some of the labs.

CDC reviews proficiency data for labs in their proficiency program nationally and internationally. For this review data are broken down many ways including what methods are used to detect tyrosine and/or succinylacetone. Dr. Matern is also providing data related to this issue. A survey of labs using tyrosine and a survey of labs using succinylacetone was done in order to understand barriers to use of the marker that is obviously more specific for the condition. Carla Cuthbert and her group at CDC concluded that obstacles to use of succinylacetone in labs are operational in nature. Some states are using the kit that does not include succinylacetone and they do not want to move to a kit that includes that until the performance of the kit changes. In other words, there is concern about the performance of the kit that includes succinylacetone in some states. Other barriers include lack of money, space and staff and equipment needed to add succinylacetone. Most labs would need to add mass specs in order to do that. Instead of adding new equipment, some states have used new methods and we may further explore that and add that to the discussion section of this paper.

Carla Cuthbert and her group and Dr. Matern are currently working on a paper which will include an analysis of the CDC proficiency data, analysis of R4S data and discussion of issues that are the main obstacles to SUAC implementation. That section is in process to include all issues in the discussion section of the paper. The first draft should be complete soon and it will be sent to Subcommittee members for review before the next meeting. There was some discussion of submitting the paper to a peer-reviewed journal. Upon publication the paper will be brought forward for consideration of action by the DACHDNC and posted on the website. There may not necessarily be any actions the Committee could take regarding this issue other than increasing awareness of the issue. An update on the status of this paper and the timeliness issue will be provided at the next meeting.

Discussion

- Dr. Bocchini asked if the performance of the succinylacetone kit is an issue. Dr. Kelm responded that the data we are seeing is that the kit is not missing babies or having an issue with screening. Those concerns were not seen in actual screening performance.

This is a good example of collaboration with the Committee, the CDC and experts in this area. Dr. Bocchini thanked the Subcommittee for their work in this area. We look forward to seeing that publication.

XI. Discussion on Future Meeting Topics

Participants suggested a number of future meeting topics, as follows:

- Dr. McDonough suggested reviewing the impact of changes in the federal government in Washington, D.C. such as budget cuts and the government shut-down on federal agencies' research program delivery.
- Dr. McDonough also recommended review of the timeliness of NBS. It is important that families who are looking at this have an opportunity to comment on the Committee's activities. For example, they could provide suggestions for improvements on the 2005 Report and suggestions on how we can do better. Dr. Bocchini agreed saying there is no question we want to move that project forward with the Subcommittee to come to some recommendations and guidance for the states and work closely with APHL and others to bring that forward as quickly as we possibly can. That is an area we need to work on between meetings to move that ahead.
- Dr. Greene recommended that the Committee discuss changes in insurance coverage of molecular genetic testing. Related to this issue, TRICARE has reviewed the new CPT codes and decided they are no longer covering approximately one hundred different tests because the codes allow identification of specific lab tests not approved or cleared by the FDA or that fail to meet TRICARE criteria for coverage. Among other things they are not covering screening for carrier status of cystic fibrosis for women. And there are probably a number of other lab tests that will not be covered. The Assistant Secretary of Defense has pointed out that members of the military who get care directly from the military can get testing not available to those who get coverage through insurance by TRICARE. Perhaps the Committee can see if there is potential for guidance for the Secretary on this matter that could be useful. Dr. Bocchini responded that the Committee has been made aware of this issue and has been exploring where potentially that might be best addressed. We will determine we might participate in addressing that issue.

- Dr. Watson said he is in complete agreement with Dr. Greene. Many providers across the country now must revert back to the last best technology of chromosome analysis since newer technologies are not covered. The issue of carriers for CF is a problem because you can't do prevention under CMS. But it is a major problem and the AMA is collecting examples of lack of access to standard of care services due to decisions by insurers over the last three or four months. It is thought that AAP and AAFP have not been involved in this issue since it concerns molecular diagnostics. A number of other groups, however, have been involved with this. The Acting Director of CMS responded negatively on this issue. Dr. Watson added that the situation is very difficult and people are misunderstanding who is obligated to follow whose policies. Physicians are required to speak directly with insurers to justify the need for a patient to have a test covered and physicians do not have time for that in this environment.
- Ms. Wicklund agreed with these comments. This is an issue in genetic counseling, especially in the prenatal area where tests that historically have been covered are no longer being covered. NSGC has some activities with regard to coverage of genetic counseling services. That update could be provided and tied to this discussion if people are interested.
- Dr. Kanis commented that this is getting attention from very high levels and this is in flux. However, he could not say anything more about this point at this time. Dr. Greene commented that it sounds like perhaps the Department of Defense may be on their way to solving this problem, but this problem affects people well beyond TRICARE so this is a general issue.

XII. Adjournment

Upon hearing no further comments, Dr. Bocchini concluded the third meeting of the DACHDNC. He thanked all Committee members, organizational representatives and members of the public attending this webinar for their work to make this Committee so successful.

Please note: These minutes are pending formal approval by the Committee. Corrections or notations will be incorporated in the final minutes