Advisory Committee on Heritable Disorders in Newborns and Children

Summary of Sixth Meeting

August 25 - 26, 2016

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) was convened for its sixth meeting on Thursday, August 25, 2016 and adjourned on Friday, August 26, 2016. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

COMMITTEE MEMBERS

Don Bailey, Ph.D., M.Ed.
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Early Childhood Development
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Mei Wang Baker, M.D.
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health

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(Committee Chairperson)
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Louisiana State University

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University of Miami School of Medicine

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California Department of Public Health
(Emeritus)

Stephen McDonough, M.D.
Retried Pediatrician

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Newborn Foundation

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Child Health and Quality Improvement

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DESIGNATED FEDERAL OFFICIAL
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Maternal and Child Health Bureau

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Valley View Family Practice

American Academy of Physicians
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Executive Director

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March of Dimes
Siobhan Dolan
Albert Einstein College of Medicine

National Society of Genetic Counselors
Cate Walsh Vockley, M.S., C.G.C.S.
Senior Genetic Counselor
Division of Medical Genetics
Children's Hospital of Pittsburgh

Society for Inherited Metabolic Disorders
Carol Greene, M.D.
University of Maryland Medical System
Pediatric Genetics

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I. Administrative Business: August 25, 2016

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

A. Welcome to New Members

Dr. Bocchini introduced four new committee members. Dr. Mei Baker specializes in newborn screening, including the use of molecular technology to do that, and public health genetics. Dr. Jeffrey Brosco is an expert in history and bioethics. He leads an inter-disciplinary team on pediatric neuro-developmental disorders. Dr. Beth Tarini focuses her research on the use of genetic resources in pediatric screening, and public health programs for pediatric screening. Ms. Annamarie Saarinen is a parent advocate and policy professional in newborn and pediatric medicine, as well as public health policy issues.

B. Welcome and Roll Call

Dr. Joseph Bocchini welcomed Committee members and other participants to the sixth meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and took roll. Voting members present were:

- Dr. Don Bailey
- Dr. Joseph Bocchini
- Dr. Mei Baker
- Dr. Jeff Brosco
- Dr. Fred Lorey
- Dr. Dieter Matern
- Dr. Stephen McDonough
- Ms. Annamarie Saarinen
- Dr. Beth Tarini
- Ms. Catherine Wicklund

Ex Officio members present were:

- Agency for Healthcare Research and Quality (AHRQ): Dr. Kamila Mistry
- Centers for Disease Control (CDC): Dr. Carla Cuthbert
- Food and Drug Administration (FDA): Dr. Kellie B. Kelm
- Health Resources and Services Administration (HRSA): Ms. Joan Scott
- National Institutes of Health (NIH): Dr. Melissa Parisi

Organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Robert Ostrander
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- American College of Obstetricians & Gynecologists (ACOG): Dr. Joseph Biggio (by phone)
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State & Territorial Health Officials (ASTHO): Dr. Christopher Kus (by phone)

- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes: Dr. Siobhan Dolan
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

C. Other Business

Dr. Bocchini said that decisions have been made about how to restructure workgroup membership, along similar lines as was recently done for the full committee. They will try to keep each of the three workgroups to no more than 20 members, with four-year term limits. Chairs and co-chairs will finalize term limits for current members and propose a timeline for rolling members off. A call for nominations for new members will be announced beginning in September. Membership for each workgroup will be finalized by January 2017.

Nominations for new committee members were due on May 16. They received a record of 43 nominations; the process for final decisions is underway. Some current committee members will transition off the committee next June.

The Timeliness Workgroup to address issues related to timeliness of collecting and processing newborn specimens. They will work to collect and disseminate timeliness specific practices from state newborn screening (NBS) programs, and to standardize communication of NBS results to providers and families. Dr. Bocchini said that the committee has worked quite effectively. As a result of their work, a number of organizations have been brought together and considerable attention has been brought at all levels to timeliness concerns. They have played a vital role in improving timeliness across the country. The committee will continue to pay attention to these issues. However, the workgroup has accomplished its goals and should be dissolved.

Recommendation: Timeliness 2.0 Workgroup be dissolved and ongoing activities related to timeliness (as required by Charter) be delegated to existing workgroups and/or the Committee.

Dr. Bocchini has accepted this recommendation, and the workgroup will be dissolved.

The Education and Training Workgroup is working to create a companion piece to ACT fact sheets that provide primary care providers (PCPs) with guidance and tips for discussing positive NBS results with parents. They are engaging in an educational outreach project in collaboration with NBS Clearinghouse/Baby's First Test.

The Follow up and Treatment Workgroup is promoting the role of clinical quality measure to promote LTFU. They are also writing a policy brief on the current state of medical foods coverage.

The Laboratory Standards and Procedures Workgroup is working to define and implement a mechanism for the periodic review and assessment of laboratory procedures utilized for effective and efficient testing for the conditions included in the uniform panel. They are also working to define and implement a mechanism for the periodic review and assessment of the infrastructure and services needed for effective and efficient screening of that.

The next committee meeting will be November 3 and 4, via webinar. In 2017, meetings will be on February 9-10; May 11-12; August 3-4; and November 8-9. Meetings have been set up through 2020, so members can plan ahead.

Dr. Bocchini reviewed the agenda and turned the meeting over to the federal officer.

D. Federal Officer Announcements

Ms. Debi Sarkar, the Designated Federal Officer (DFO), reminded the committee members that they are advisory to the Secretary of HHS, not to Congress. She asked that all committee members check with her before agreeing to any interview touching upon the committee's work. She also reminded them of the requirements on disclosure and recusal related to financial interests.

She also reminded members that the committee's activities are guided by Federal law. They must follow FACA requirements, including holding open meetings and providing advance notice in the Federal Register of public participation opportunities.

E. Approval of May meeting minutes

No committee members had additional changes to make to the minutes. Some revisions had been sent in to Ms. Sarkar previously.

By roll call vote, the minutes, as corrected ahead of time, the minutes were approved unanimously.

II. Pilot Study Workgroup Recommendation on Required Data Elements

Dr. Bocchini said that this recommendation has previously been distributed to committee members. Some members requested additional information on why the workgroup made some of its decisions for the policy statement.

They decided to create this workgroup to see if they could standardize the information required to bring a condition forward for evidence review. The committee has nine months to make a decision once they initiate the external evidence review. Thus, they want a strong process in place to support nominations coming forward. They wanted to, at least, define the minimum information required to make a nomination.

In this discussion, Dr. Bocchini said he wanted to provide additional information about one particular part of the recommendation: that data should be available from pilot studies involving population-based screening of identifiable newborns. Specifically, the recommendation requires that the pilot study be sufficiently large to identify at least one true positive clinically affected newborn for the condition under consideration.

Scott Shone, PhD, a member of the workgroup, spoke to the committee on how the workgroup reached its conclusions. He works for the New Jersey Department of Health.

Dr. Shone said that, in talking with his colleagues from around the country, he feels there is consensus around the one case requirement.

The Pilot Study Workgroup was trying to find the minimal necessary data to move a nominated condition for full evidence review. The goal is to identify conditions for which the federal government should recommend screening of all newborns. He noted that the statute now requires that the evidence review be conducted within nine months, which makes proper identification of conditions more necessary.

When considering new disorders, they must determine more than just whether there is a lab test. They must also consider how to identify affected newborns and how to get them into treatment.

It is not sufficient to just look at retrospective specimens. That is not real time, and does not constitute timely identification and results. Simply identifying a single child is only one part of the entire process. The process must also be able to get identified children into treatment.

Dr. Shone said that, often, once newborn screening is implemented, more cases are found than expected. If there is no system in place to get the children into treatment, then simply screening and identifying them is a waste.

He said that screening creates a larger population of impacted people beyond just those showing symptoms of a condition or disease. He stressed the importance of having as complete a set of data as possible, in order to have both accurate numerators and denominators.

This is why it is so important to have a uniform process that not only screens, but also diagnoses newborns and gets them into treatment. "It's imperative that the committee's process be uniform," he said. Historically, the process has varied, but the committee can change that. In addition, a lack of uniformity in the process makes the entire process look haphazard. As a result, there is then a danger of looking haphazard with review results.

If a pilot study does not have a case, and the condition goes into evidence review, data will be lacking. He said it is "pure uncertainty" to go that far.

Thus, Dr. Shone said, finding one case shows that the entire NBS process could work to identify affected newborns. It also demonstrates that the diagnostic process can actually identify a true case from asymptomatic screen positives, proving that the entire system works, and not just the screening. Finally, it also will create uniformity for the entire committee review of nominations process to move a condition to evidence review.

Committee discussion

- Dr. Lorey and Dr. Tarini both complimented the presentation. Dr. Tarini said that, if the processes do not work, the benefits intended will not be delivered. She thinks there is an issue for the committee to consider, though. If the presence of one case is important because it demonstrates how the process works, then the evidence review should consider how that process takes place. To date, the committee has not really looked at that. She questioned whether the process needs to be assessed now as part of the evidence review.
- Dr. McDonough said that, during the GAMT discussion the committee talked about delaying further work by a year while more evidence was presented. Similar discussion took place about SCID. As for SCID, the delay only resulted in finding the needed case a year later. He said that they do not need to add unnecessary barriers to conducting needed evidence review of conditions. Dr. Bocchini said that the issue involved here is not the same as the issues involved in either the GAMT or SCID discussions.
- Dr. Bocchini said that the laboratorians need the evidence of this one case to ensure that the test in question is effective in identifying affected newborns.
- Ms. Wicklund said that she appreciates getting a better understanding of the fuller picture. She said that the group does not know the harm of implementing a test for which they do not know the implications. It is dangerous to start feeling like they need to approve everything.
- Dr. Brosco asked what would happen if they decided to go on with evidence review without that single case, and no case came up within the nine months of the review process. Ms. Scott said that the statute requires the committee to still vote. She is concerned about putting something forward in the hopes that a case is found in the nine months, given the amount of evidence review work that needs to be done in a relatively short period of time. Ms. Sarkar

said that the committee can still ask the workgroup to continue looking for more evidence even if the vote is no.

- Dr. Matern said that proponents need to be more careful in identifying exactly what disease is being screened for. In the past, such as with PKU, they have found other things in the process. He also questioned whether, for purposes of this discussion, it truly has to be a new case, or a prospective finding from a previously collected sample. Above all else, he wants clarity on what the committee decides. Finding rare and extremely rare diseases is very difficult.
- Dr. Bailey thinks it is "a little unfortunate" that they are pushed by the nine month requirement and are left with only a yes or no vote at the end. Given that, they have to recognize several things. They are setting a very high bar for conditions to move forward to evidence review; however, slowly down the process may be appropriate in some cases. There are no natural funding streams for conditions before the committee votes on them. These things will need to be done on a consent model, which means it is not true population health screening. He thinks it will make it very difficult for new conditions to be able to meet this requirement.
- Dr. Shone said that it is incredibly dangerous to suggest getting data outside the consent model. The purpose of the committee to add a condition to the RUSP is to show that there is data for the condition. Just because there is a test available does not mean that everybody should be subjected to that test.
- Dr. Bocchini does not think the committee has considered adding anything to the RUSP without pilot study data, after the first 29 conditions.
- Dr. Tarini said that there seems to be a presumption that a case will be found; it's just a matter of time. She is not so sure about that for all conditions. Predictions of how many cases will be found tend to be based on previous population screening, and different prevalence levels turn out to be true once real screening take place. In today's health care system, the lack of health outcomes data prevents retrospective data from being truly usable. It is unknown if the condition is under or over diagnosed in the past, and there is no thorough, final diagnosis of health years later.
- Dr. Baker said that they should work to find data for moving forward, because you never really know what you're going to find until you look.
- An organizational representative said that pilots are funded based on an expectation of incidence. He warned that states will start setting mandates based on their own experience, which goes beyond the committee's intention to make recommendations before state mandates occur.
- Dr. Ostrander said that a prospective, blinded study is always preferred. However, that is not always possible. Action can be taken based on a retrospective study with a reasonable level of certainty, based on stored blood spots. He agreed that unexpected harms will be easier to find in a prospective study. With a retrospective study, they can do an analysis of the expected harms. For most conditions, he said, those harms will be fairly low.
- Dr. Greene talked about the pitfalls of harm. With neuroblastoma, some babies underwent major abdominal surgery for something that was later found to regress naturally. This is an example of clear harm that occurred without a clear understanding of the underlying condition. She supports creating a uniform standard to apply to all conditions, as this recommendation does. She stressed that just having the one case will not fully teach about all of the potential harms; many cases are needed for that.
- Dr. Tarini said that this is public health, and not straight medicine. This means that the screening would be mandatory. In medicine, decisions are made about what is best, and patients have the option of going forward. In this structure, the government will be mandating what is to be done, and parents will have a narrow window for opting out. In

addition, it is hard to remove a disorder from the screening process. In fact, there is no precedent for doing that should no case be found using a given test. She also said that a condition not sent onto evidence review can come before the committee another time.

- Dr. Matern talked about published literature on patients who are subjected to false positive test results. He thinks that much can be learned by comparing studies already done.
- Dr. Brosco said it sounds like there is a disagreement about whether there is something different scientifically in finding a condition in an older specimen than in doing so prospectively. Dr. Shone said that the difference is what finding the case shows. Doing so retrospectively simply shows that the test is valid. Doing so prospectively shows what the entire program and process does in real time, and whether it works in real time.
- Dr. Matern said that the goal could be met by "throwing in" the old samples, which are known to be positive, into the prospective study. They know what the system can handle because of what is happening already in the screening program. He agreed that no conditions should be added to the RUSP until all of the processes involved for that condition are set out.
- Dr. Brosco asked if, after having to vote no due to the lack of a single case, the committee could agree to meet and quickly vote yes once the single case is found at a later date. Dr. Bocchini said that this is a separate question, and is not up for discussion today. The current discussion is solely about whether it is an acceptable standard to require that a single case be found.
- Dr. Bailey would rather see them identify what they want to learn from the positive case, rather than set an "artificial" goal of a single case. The fundamental question is what they want to know from identifying that first case. Dr. Bocchini agreed that the single case does not answer all of the questions. However, it does answer whether the test is validated.
- Dr. Greene said that the people in the lab are asking to have that one case. She thinks they also need to have the additional information to which Dr. Matern referenced, which requires more than the single case, before a recommendation for addition to the RUSP can be made.
- Dr. Tanksley said that having a screened positive go through the process proves more than just an analytical validation; it proves the entire process works.

VOTE

Ms. Scott made a motion to vote on the recommendation, and a second was made. No one made a move to abstain or recuse oneself from the vote.

The final vote was 12 committee members in favor, and three against.

In favor: Bailey (with reservations); Bocchini; Baker; Brosco; Cuthbert; Kelm; Lorey; Mistry; Parisi; Scott; Tarini; and Wicklund (with reservations).

Against: Matern; McDonough; and Saarinen.

After the vote, Dr. Bocchini said that they will now work to get the full recommendation published. He assured a committee member that her editing suggestions were included. Ms. Sarkar said that the revised version was included in the briefing book, and offered to send it out again.

III. Public Comment

A. Stephanie Boussard and her daughter, MPS 2, 4 & 6

She spoke about MPS, which is a degenerative disease that affects every organ. It usually takes months or even years to fully diagnose the disease, during which time additional harm can occur. She thanked the committee for approving screening for some forms of MPS.

Early diagnosis and treatment will improve quality of life and reduce harm to organs in the patient.

Including the forms of MPS for which FDA has approved testing in screening is critical to getting parents more access to screening and treatment tools.

Her daughter was diagnosed at six months, because she identified a bump on the child's back that the pediatrician had completely ignored. Such an early diagnosis is highly unusual. She said that she was lucky, because she knew the disease progression and knew what to expect and what to do as symptoms arose, such as pain from walking and lack of stamina.

She stressed that most children with MPS are not diagnosed until between ages three and five, at which point deterioration is irreparable.

She asked that screening for MPS 2, 4, and 6, which do have FDA approval, be included in the next round of nominations.

B. Shannon Zirzan, Spinal Muscular Atrophy (SMA)

Her son has this condition, which is the leading genetic cause of death in infants. On behalf of Cure SMA, she commented on adding SMA to the uniform screening panel. She said that "we are now at an exciting precipice" in achieving cures for this condition.

Diagnostic delay is very common. Early identification can prevent this, along with the physical declines that occur during the delay.

One study has shown that infants with SMA Type 1 appear to be developmentally fine, and only reveal problems around age three months. Pre-symptomatic treatment is only possible with pre-symptomatic identification. This is why newborn screening is so important. She asked that the committee favorably consider the nomination of this condition to be added to the screening panel, especially in light of the new treatments.

C. Kristen Stevenson, Muscular Dystrophy Association

Ms. Stevenson explained the role of MDA in funding research and pushing policy changes. She expressed appreciation for the addition of Pompe Disease. She said that both SMA and MPS are strong candidates to be added to the uniform screening panel. The community is already preparing for newborn screening in these diseases. Precision medicines are under development to treat them, as well.

The causative gene for SMA was only identified a decade ago, and cures addressing that are already becoming available. They hope to see the first drug filing for SMA using gene therapy.

She stressed that time is of the essence to expand newborn screening for these conditions.

D. Kim Tuminello and Heidi Wallis, GAMT Deficiency

Ms. Wallis showed a series of pictures of children affected by this disorder, in the US, Great Britain and Canada, including her own two children. Her daughter was first diagnosed with autism, and then with GAMT. She talked about the child's lifelong battle with seizures, and said she will require lifelong care.

Alternatively, her son was diagnosed at birth, and was put on medication almost immediately. As a result, he scores cognitively in the typical range for his age of five.

In other words, GAMT diagnosed at birth leads to treatment that results in a normal life. She said that newborn screening also works. Evidence has been established that the amount of this endocrine does not change over time. Thus, retrospective studies could be conducted on stored blood spots.

Ms. Tuminello repeated her public testimony from a previous meeting on the need to add this disease to the panel. She understood the loss by a single vote in May. At the time, she was discouraged by the requirement to find a single positive newborn in the pilot study in Utah. However, shortly after the May meeting, another positive baby was born in Austria.

She related her own experience of trying to find out what was wrong with her son, through months of looking for a diagnosis. Her son was the first person in the US diagnosed with GAMT.

She said that families are depending upon the committee to add this condition to the screening panel, and said that childrens' lives are at stake.

E. Dr. Nicola Longo and Dr. Marzia Pasquali, Screening for GAMT Deficiency

Dr. Longo said that they have seen quite a few patients with this condition, and asked that screening be added to the uniform panel. There are new data on the occurrence of false positive results. After a year of screening, they found one false positive out of 60,000 screenings. That occurred in New Zealand, which had the false positive out of 45,000 screenings.

The positive screening in Utah came out of 30,000 newborns screened.

Previously, screening has been done on urine. It is now known that testing blood is more accurate.

Screening at birth allows for faster diagnosis and the start of treatment. Such early treatment has also been shown to have a very positive on patients' lives. Treatment needs to be tailored for every patient, especially since it is partially based on the diet for these newborns.

He asked that the committee keeps GAMT on its radar, and approves it soon.

Dr. Bocchini said that the committee is willing to work with the researchers to include the new information in a re-nomination packet soon.

F. Jackie Sizeman, Newborn screening education for midwives

Ms. Sizeman said that her organization has created guides on newborn screening for those engaging in home births. They interviewed midwives and parents who are already involved in home births. They found that these midwives are "severely limited" by the cost of and complication in conducting screening. Midwives only perform the heel prick only if they can

afford the screening cards. Otherwise, they refer the family to a physician; however, often that never happens. This intensifies the lack of information parents receive on the importance of newborn screening.

She noted that the number of women choosing home births is rising every year. She called for greater partnering and support of midwives to strengthen and expand screening of that population of newborns.

Dr. Bocchini said that this is a very important issue, and said that he would be interested in speaking with the public witness further at a later time.

IV. Molecular Analysis to Enhance Newborn Screening

Michele Caggana, ScD, FACMG
Deputy Director of the Division of Genetics
Director of the Newborn Screening Program
New York State Department of Health
Faculty Member, Wadsworth School of Laboratory Sciences

Dr. Caggana talked about newborn screening in the light of advances in molecular screening. She said that newborn screening is intended to assess risk for disease. Tests must be universally available and timely. The goal is to find the one baby at the highest risk for the conditions being screened for.

The cost of genome sequencing is declining. However, she said, it is still quite expensive. It would cost her program in New York $10 million per instrument, and over $200 million per year, plus overhead.

She looked into whether molecular testing adds value. The goals would be to increase the sensitivity of a primary test, and have an effect on specificity. Over time, it would also be hoped that predictions based on phenotype could be improved. That could mean better treatment for asymptomatic children. Also, sometimes clinicians use the molecular data for diagnosis, rather than applying additional tests.

Most of the time, newborn screening programs are using second tier molecular tests, primarily to increase the sensitivity for cystic fibrosis (CF), and to clarify ambiguous results.

She has a pilot study on spinal muscular atrophy underway.

In looking at going in this direction, they must consider the cost and the value added. Other considerations include the impact on timeliness; staff time and qualifications; where and how long to store and analyze data; instrumentation requirements; and other practical logistical considerations. She also posed the question of whether going in that direction turns the screening programs into diagnostic laboratories rather than screening ones.

She described how, over time, DNA sequencing has moved from a time-consuming “art” to a faster, computer-based system.

For newborn screening, she said that they need to have relatively cheap, reliable instrumentation in quantities large enough to accomplish the daily job.

Today, single genes are genotype to give an assessment of an infant's health status. Some experimental work is ongoing for sequencing a panel of genes. Some companies are offering panel screens for newborns outside the public health infrastructure. Eventually, the goal could be to sequence everyone's genes, and not just newborns.

Dr. Caggana said that, since 2006, her program has screened for Krabbe Disease. They do the biochemistry test. Positive results are re-tested. Molecular testing is done on positive samples. This process has resulted in a 41.3% reduction in referrals for children who do not actually have the mutation. This has not only decreased the number of referrals but also decreased familial anxiety.

The major challenge is determining whether any given variant is pathogenic. In newborn screening, they are looking at apparently healthy babies who may be at high risk of getting ill. Trouble occurs when a variant is likely to be pathogenic, of unknown significance, or likely (but not certainly) benign. She said that the question is what to tell these families, in order to reduce their anxiety.

For example, most CF referrals do not actually have the disease due to a high rate of false positives. Thus, they screen for a small number of mutations known to cause CF. Most babies who are referred have two mutations. A small number of single mutations are known to cause CF, so babies with just one mutation are also referred for more diagnosis and treatment. Those with high IRTs are also referred. Between 2010 and 2013, they had 900 referrals altogether, which picked up between 29 and 65 cases.

She showed evidence that increasing the panel and also using sequencing finds more cases.

As a result, New York has proposed developing a TruSeq panel including all mutations found in diagnosed cases. That panel will first look at all of the true New York cases. Now, all babies with one mutation would then have their entire genome sequenced. She expects to reduce the referral rate from 900 per year to only 100 per year.

Doing this will also increase turnaround time. However, CF is not really a time-sensitive. Thus, taking extra time to notify parents will be worth having caused fewer parents anxiety due to false positives.

She then talked about next gen sequencing (NGS) and severe combined immunodeficiency (SCID). This is a spectrum of disorders that can only be differentiated by identifying causative mutations, and involves many genes. Immunologists can provide better care when SCID causative mutations are known quickly. Right now, this is done post-analytically by the clinicians. Screening labs could provide the mutation early, when the clinician sees the family. When public health identifies the mutation, then quality is ensured.

Right now, the process of identifying the condition is slow and iterative. The pilot aims to validate two platforms for a 39-gene NGS immunodeficiency panel. They will be looking at whether the NGS is useful in shortening the time to diagnosis, which could lead to fewer specialist visits and earlier, more targeted treatment. Long-term follow-up will be initiated for these children. They also want to create and disseminate educational materials for parents and providers to help them access state programs.

Right now, they are doing retrospective identification to create a model pathway.

She described what the pilot program is doing in sequencing all known NBS genes. They are looking to establish a NBS core, but this is still a ways down the road.

When looking at sequencing in the context of screening, they have to look at whether this actually makes things easier or better for families. They also have to consider the fact that screening programs will now become diagnostic, and the added burden on the program and on clinicians this could cause.

She said that the NBS and public health programs are a community of collaboration. She believes that this can be done in a way that can help everyone.

The Molecular Subcommittee's mission is to ensure continuity and responsible growth of emerging molecular technology within the NBS public health environment. Several states have participated, including Washington, Michigan, California, New York, Minnesota, Iowa, Wisconsin, Texas, Massachusetts, and Puerto Rico. They became an official subcommittee in 2011.

She said that the subcommittee aims to facilitate a collaborative educational environment, and to provide assistance to anyone wanting to implement molecular technology in a NBS program. It is clear that this is on the mind of many public health state laboratories, as demonstrated by applications for participation in the group's training programs.

The subcommittee has engaged in a number of outreach activities, including training programs, workshops, and a website. They are planning a meeting of this to take place in the first quarter of 2017.

They are also getting ready to launch a second molecular survey, to find out the status of testing in laboratories across the country. The last such survey was six years ago.

Committee Discussion

- Dr. Greene noted that sequencing finds about 98% of the babies affected by CF. She thinks this decreases the sensitivity, unless they continue to follow up with the high IRT group independently. Dr. Caggana said that CF providers have expressed comfort with the babies who will be missed, but it will not be by much since some babies are referred twice.
- Dr. Mei Baker brought up concerns over increasing the sensitivity as opposed to the specificity.
- Dr. Caggana told Dr. Greene that providers have repeatedly told them to do more screening for babies with meconimum.
- Ms. Scott asked about overall capacity across the US. Dr. Caggana that about 43 or 44 labs are about halfway there, with screening for SCID. Most states do not have an entire lab devoted to newborn screening. There are workplace and personnel limitations. There is work to be done in taking the leap from doing panels to doing the sequencing.
- Dr. Baker talked about how states could make the costs of doing the next gen sequencing more affordable.
- Dr. Parisi said that CDC and NIH want to get a handle on where the states are in these areas. There is a big need, and they want to get an assessment of what states are where, and who needs what help. They want to educate those who are not as well-informed.
- Dr. Tarini said that, as this moves forward across more states' programs, the states "take a hit" on the quality metric of reporting all tests within seven days. She suggested that they keep in mind that future recommendations do not hinder potential innovation.

- An organizational participant (Dr. Watson?) said that most labs will not have someone who is board-certified in molecular screening. As a result, to best evaluate variation, greater data sharing will be needed, and he hopes this occurs outside the public health labs as well as across them. Dr. Caggana agreed that they need to figure out how to close the loop between diagnosis and long-term treatment.
- Dr. Matern would prefer not to see the variance. He wants to know the genotypes causing disease, because the variants are of uncertain significance.

V. Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) (Panel Discussion)

Don Bailey, PhD

Dr. Bailey explained that representatives of four funded centers will explain what their centers are doing, and present a key finding from what their center is doing. They have not been focusing on newborn screening as much as using sequencing on newborns in different contexts.

He said that NBS is an evolving public health program that is constantly faced with new challenges and opportunities. The program seeks to advance understanding of the causes of diseases and appropriate treatments. They face challenges in getting evidence for presymptomatic treatment of rare disorders. Advocates are constantly pushing for expanded screening. State budgets limit their capacity to conduct screening and follow-up. New technologies for screening are cropping up, including the possibility of whole genome or whole exome sequencing.

There is now the opportunity to explore, for research purposes, the possibility of using genome sequencing in the newborn population. In 2010, NIH held a meeting focused on NBS in the genomic era. Experts agreed that it is important to evaluate genomic data in newborns using NBS as a framework. They also determined that it is important to prioritize clinical validity and clinical utility of this, not just the analytical validity. Along the way, ethical, legal and social concerns must be addressed as well.

In parallel with that meeting, quite a few articles have come out about sequencing in newborns. These articles have addressed many of the questions brought up in the NIH meeting. The discussion in the literature is important and has been robust, and should continue.

NIH issued an RFA in 2012 titled Genomic Sequencing and Newborn Screening Disorders. This was a U19 grant, which means it is a cooperative agreement. That means there is a lot of interaction with the funding agencies. The centers were required to address one or more of the following questions:

- For disorders currently screened for in newborns, how can genomic sequencing replicate or augment known newborn screening results?
- What knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide?
- What additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns?

Each center was also required to have a sequencing component; a clinical research component; and a component that addressed ethical, legal and social implications. The three components were to be built into their grant applications.

There were four awardees:

- Robert Green, MD and Alan Beggs, PhD, Brigham and Women's Hospital, Boston.MA
- Stephen Kingsmore, MD, Children's Mercy Hospital, Kansas City MO; Rady Children Hospital, San Diego, CA
- Jennifer Puck, MD, Barbara Koenig, PhD, and Pui-Yan Kwok, PhD, University of California, San Francisco, CA
- Cynthia Powell, MD, MS and Jonathan Berg, MD, PhD, University of North Carolina at Chapel Hill, RTI International

Each of these awardees presented at today's meeting.

The centers were not originally funded as a network. Thus, they could not propose collaborative activities through the applications. However, the cooperative agreement has allowed for this coordination. They have working groups on common data elements and ethical issues, as well as regular meetings on various topics and bi-weekly conference calls of all investigators.

A. Determining Medical Actionability of Gene/Disease Pairs and Relevance to Newborn Screening

Cynthia Powell, MD
Professor of Pediatrics and Genetics
The University of North Carolina at Chapel Hill

Dr. Powell said that her project looked at the potential use of screening to follow up on children with potential issues identified in newborn screening. Historically, NBS has been industry and technology driven. With the advent of next generation sequencing, there is the potential to exponentially increase the number of conditions that could be detected. One of the big challenges is how to be good stewards of that information, and how to utilize it in a useful way.

She explained how to collect and prepare a blood sample, which varies depending upon what is being looked for. She said that this targeted sequencing method can be used to find a single condition or a panel of conditions. The bioinformatics involved is a huge component of next generation sequencing. Even though every gene is being sequenced, the computer can be told to only report the targeted genes or variants.

UNC has a "Binning Committee" to determine what conditions to look for. This is a group of ethical and medical specialists with interest in the field. They looked at the morbidity of the various known genetic diseases, and whether a condition could lead to death, chronic problems, developmental issues, or if the condition will have little impact on future life. They also looked at how effective interventions are in preventing harm when a genetic variant is found. In addition, they looked at whether the treatment is minimally or highly invasive or difficult to implement. Finally, they examined what clinical practice guidelines might exist for treating that condition.

She presented several examples of conditions, and the scores they received from the committee based on these considerations.

There are 14,350 human genes in the OMIM database, and approximately 4,800 with phenotypic description and known molecular basis. So far, her group has scored 790 gene/condition pairs. Of those, 499 have been finalized and 291 are pending further review and binning (or scoring).

They have concentrated more on gene/condition pairs with childhood onset. They have also focused upon whether something can be done when a condition is discovered. They have identified 307 pediatric actionable conditions so far.

They have a group of patients with known conditions which were picked up through newborn screening. They will look whether whole exome sequencing will pick up those conditions.

Another group of healthy children will also be addressed, through the UNC clinic. The researchers will be looking at how families make decisions about genetic sequencing when the child appears to have no health problems.

They have developed a decision aid tool for parents in cooperation with RTI.

B. Implementing Universal Pediatric Precision Medicine in San Diego

David Dimmack, MBBS
Medical Director
Rady Children's Institute

Dr. Dimmack said that this project is taking place in San Diego and Kansas City. The focus is on implementation of science in precision medicine in a learning healthcare system.

Fourteen percent of US newborns are admitted to a NICU. This is a huge burden on the care system, and very stressful for parents.

The 8,000 known genetic diseases affect about 3% of children. They are the leading cause of death in infants, and in both NICUs and pediatric ICUs (PICUs). In this situation, the environment is far less likely to be the result of disease (although zika may be an exception). He noted that 80 years of benefit could be achieved with only one childhood case.

He showed evidence from one case, of an infant with acute liver failure. Within an hour, they had brought the parents' and infant's blood sample to the lab. The sequencing was done in just under 24 hours.

The biggest challenge to them in diagnosis is making sense of what the clinical presentation actually is. They are working to pull more usable information from electronic medical records.

In the case being presented, just through computer analysis they brought the number of possible diagnoses down from millions to 341; continued computer analysis brought that down to two. As a result, 26 hours after the child was found to be ill the diagnosis was found. There was easy treatment available; the child is now 36 months old and ready to live a normal lifespan.

He posed the question of whether this can be scaled up to meet the population need.

Of the first 115 babies screened, they had a 57% diagnosis rate. In about a third of those cases (13), care was changed in response. The most common change was to recognize that the child had a fatal condition, and care was moved to palliative. He said that, for those six children, moving to palliative care can be considered to be a positive move as parents did not feel obligated to take heroic measures, and their emotional load could be better managed. In another three cases, major morbidity was avoided.

His facility has a ten-year vision for pediatric precision medicine. He noted that minorities are under-represented in research. He estimates that, in San Diego County, there are 22,000 children with undiagnosed genetic diseases. They think they can sequence about 8,000 genomes a year. That will lead to diagnosing just over 1200 new cases a year.

They hope to be able to do 24,000 sequences a year in 10 years. That would mean that about 4000 new diagnoses per year could be made. They also want to provide evidence that genomic sequencing makes a difference.

C. NSIGHT NBSeq

Barbara A. Koenig, PhD
University of California San Francisco

Dr. Koenig said that her project explores the potential applications of whole exome sequencing (WES) to public health newborn screening. Specifically, they are evaluating the feasibility of WES to replace or augment tandem mass spec (MS/MS) for metabolic disorders.

Project 1 involves taking 1,570 dried blood spots from the California Department of Public Health Biobank and actually doing the sequencing. They are doing comparisons to determine whether the original lab diagnoses were correct. They found 203 cases where metabolic disorder cases were false positives or false negatives. They are annotating the variants in a set of about 90 primary metabolic genes.

Project 2 builds on the success of NBS for early detection of SCID. They looked at whether WES could identify actionable conditions prior to the onset of severe infectious complications. They are enrolling 50 individuals with poorly characterized immune defects who were born in California after 1982.

Project 3, which she leads, looks at how next-generation sequencing will enhance, challenge or transform traditional state-mandated NBS, and how it should be doing this. They are trying to get at legal challenges and other normative issues. They want to create a national policy board that will develop and disseminate recommendations about the appropriate use of whole genome analysis in newborns.

Most parents do not even remember having NBS. She thinks the starting question should be the appropriate balance between parental consent for NBS and public governance. Thus, in addition to the NSIGHT project, they have another project on Deliberative Community Engagement, which they call the Consider Project. The purpose was to generate informed, deliberative, and community-based recommendations to inform critical and time urgent policy decisions.

Deliberative community engagement could allow NBS to move past the limits of individual informed consent. In a community setting, public health officials could debate and discuss tradeoffs of screening with the possibility of false positive test results. They could also address broad public concerns such as eugenics and the privacy/research benefit tradeoffs.

She said that the presence of special interests at meetings such as this is fine. However, “normal individuals” are not present at the same time. The deliberative community engagement process would solicit those voices, so that they would be heard as much as the special interests. During the process, participants receive briefing and educational materials ahead of time.

During a recent such event in California, there was unanimous agreement that NBS should be mandatory. Discussions took place over the course of a full weekend, and were run by professional facilitators.

Several recommendations came out of the discussions:

- Officials should clearly separate the activities of the NBS program and asking permission for the biobank program.
- The group was more divided on allowing return of results from the biobank.
- Samples collected without permission prior to 2015 should not be destroyed; not require contact or permission to be used; and should be the subject of public education to raise awareness.
- It is appropriate for existing samples to be used for external research to benefit health and wellness.
- Information that enables full transparency makes the biobank trustworthy.
- A community advisory board should collaborate with the state about how to return results from the biobank to the families.

In addition to the over 600 blood spots that have been sequenced, her group has published several papers on related topics.

D. BabySeq

Robert C. Green, MD, MPH
Director, genomes2people
Division of Genetics, Department of Medicine
Brigham and Women's Hospital

Dr. Green said that their approach is looking at the outcomes of sequencing babies, both sick and well, whose parents want the sequencing to be done. They are looking at the impact upon individual and public health of sequencing under a lot of different situations, not just babies. He explained that the BabySeq study is just one in a series of projects, ranging from babies to adults.

The BabySeq Project is a pair of parallel randomized clinical trials. They hope to enroll 240 NICU infants and 240 healthy newborns. They will be randomized into groups that provide the standard of care plus an enhanced family history with or without genome results. They will then be tracked, using the electronic medical record, to determine physicians' treatment into the future.

The first question is whether parents even want their healthy babies to be sequenced. He found it fascinating that a large proportion of these parents expressed some level of interest.

There is no standard for what categories to report for baby sequencing. They tend to report everything, even non-actionable items.

For the well babies, they are reporting information on risks for childhood onset diseases, and the carrier status for those diseases, as well as pharmacogenic information relevant to pediatrics. NICU babies get all of that information plus genes associated with the infant's clinical features. There is also an option to focus on gene variants related to the infant's care.

They also had to figure out how to report the information in a usable way. They developed a one-page summary for the genome report, which would accompany a fuller report. He said that primary care physicians found this to be very useful.

The next question is what genes should be reported. Their IRB was not comfortable with reporting adult-onset diseases, so they restricted themselves to childhood-onset ones. This resulted in 1500 being curated, of which around 900 genes were actually reported back to the families. They also created specific criteria for including variants. They reported back variants that are known to be pathogenic, likely to be pathogenic, or of uncertain significance.

People are very hesitant in both categories to sign up for the research project. For the NICU cohort, they are running at a 6.7% enrollment rate. He said that the low rate is due to the disclosures required by the IRB, especially the possibility of discrimination when the baby is an adult. A similar enrollment rate is seen among the healthy babies. Most people choose not to enroll over concerns over confidentiality or privacy, and fear of insurance discrimination. He noted that a lot of progress could be made if that fear could be eliminated.

They created a deviation from the protocol to alert parents of any adult-onset disease information to the parents, if they want to hear the information. This came from a case of a child with the BRCA2 gene, which can mean a higher propensity for breast and ovarian cancer. They were able to determine that the variant came from the mother, which had led to an ethical dilemma about telling her of her health risk. In this case, the mother was grateful to learn the information. She had not initially reported any family history of cancer; it was revealed after the test results.

E. Panel Discussion

- Ms. Wicklund was told that babies were identified through the sequencing who would not have been identified from the regular process. The effectiveness is much higher for the rapid genome than for the regular standard of care, according to Dr. Dimmack.
- Dr. Dimmack told Dr. Brosco that clinical utility of sequencing is harder to show.
- Ms. Wicklund asked how they made the jump to identify the single gene for the diagnosis. Dr. Dimmack said that they look for an overlap between the disease for which they are looking and the gene variants known to be responsible.
- Dr. Koenig asked if, with the liver disease case, it could have resolved itself. Dr. Dimmack said that the child would probably have ended up in organ failure if the intervention had not occurred.
- Dr. Parisi asked about the logistical challenges in enrollment and recruitment. She asked if they had developed any strategies that others could use. Dr. Dimmack said that he could only think of one case where someone refused rapid sequencing. The experience is very different elsewhere. He said that the concept of consent is not really valid in an ICU setting. The opinion of the ICU doctor will influence the parents considerably. Particularly among minority populations, parents are not interested in their children being research subjects. Uptake increases when it is presented as a new and exciting advance. He said that they need to find some way around this artificial IRB-imposed hurdle.
- Dr. Green agreed. He said that framing the request is very important. Other sequencing programs are getting much higher levels of consent. Using a randomized clinical structure, as he is, really emphasizes the research nature of the project, and makes it less clear that the information will be used to help the child.
- Dr. Dimmack said that he has been involved in other studies with similar issues. They only had a 1% uptake for a study simply to take family histories on the computer. In another study, they are having a real problem, due to IRB-imposed conditions, on getting people to agree to testing based on the standard of care through the protocol, but they will pay money to get tested outside the protocol.
- Dr. Bailey said that parents are driven by a whole host of issues. This goes beyond informed consent, and should be involving informed decision making instead. He thinks there should be more study on these issues.
- Dr. Dimmack told Dr. Baker that the 57% diagnosis rate is based on the sequencing. It does not include chromosomal abnormalities. Testing and result delays are actually a problem right now.

- Dr. Tarini asked what should be done in response to the poor uptake for research purposes. She asked if informed consent should be tossed or circumvented in some way. Dr. Powell thinks that everyone should be educated on NBS and genetics ahead of time. On the social policy end of things, policymakers need to address things such as insurance discrimination.
- Dr. Koenig said that informed consent is asked to do "way more work than it can possibly do" in the human research arena. This is why she favors larger ways of determining community consent, rather than getting the individual signature on the bottom line.
- Dr. Dimmack said that another complication is requiring that informed consent forms be translated into the patient's language before it can be signed. In San Diego, that means over 40 languages. He thinks something needs to be done to improve the informed consent process, moving away from signature requirements as well as how sleep-deprived and overwhelmed the parents might be on a particular day.
- Dr. Green is troubled by excluding things unless they only occur 1/100 times, especially since PKU is 1/50 cases. Dr. Dimmack agreed that this is a problem, which is why it is important to have algorithms in place to find everything.
- A participant said that a lot of the refusals could be avoided by quantifying the risks, and showing that the risk exists, but is very, very low. As for things such as insurance discrimination, Dr. Green noted that, even though health insurance is available regardless, there is no way to predict what will be the case when this newborn reaches 18 years of age.
- Dr. Brosco said that the control groups are very important to learn the added benefits of genome sequencing. There are ways to use community-based consent, as have been shown by some studies.
- Dr. Green said that there are companies using research standards to circumvent clinical care. They are offering a product and having participants sign a research protocol. They are charging as much as $25,000, which implies a certain value, and there is a commercial IRB in place. The danger is that this is the kind of thing providing all of the "evidence" available, which gets in the way of researchers such as those on the panel.
- Dr. Dimmack said that, while they can now get funded randomized trials, the standard of care has changed drastically over the last six years. This makes it hard to determine whether the sequencing is driving any change to the standard of care.
- Ms. Saarinen said that the information from the NICU population could be used to support and to provide additional information to babies in the well setting, especially before childbirth occurs and the parent becomes overwhelmed. If this becomes a population health "thing", she asked how what is happening in the well child setting could impact what happens in the NICU. She also asked if population-wide full sequencing of babies is a good idea.
- Dr. Koenig said that her project aims to determine whether sequencing is actually good enough to take the place of what is currently being done, or if it only has utility as a backup, secondary test. "We don't have the answers" to those questions yet, she said.
- Dr. Dimmack said that the cost of analyzing the data is two to three times the cost of doing the sequencing, because so much is not yet automated. There are also additional costs of knowing your genomic sequencing, both financial and psychological, growing up. He said that those future costs are unknown, although other disease research indicates that it could very well be positive to know about these facts. He said that they also have to look at the possibility of false positives, and the possibility of doing harm by implementing unnecessary interventions.
- Dr. Dimmack added that some portion of those children diagnosed with autism do have treatable conditions. However, the research first needs to be done before wider screening can take place to find them.

- Dr. Powell said that not enough is known about the penetration of certain rare diseases. There are some very old people with genetic variations who have not developed the condition indicated.
- Ms. Saarinen talked with the researchers about changes in technology, and noted that ultrasounds are now routine. Dr. Green agreed.
- Dr. Tarini pointed out that ultrasound became more routine as the technology improved. That is not where genome sequencing is today. Genetic testing today is still very much in its beginnings, and probably needs to get much better before it can be routine.
- Dr. Koenig said that the impact of test results upon families, and not just the babies, is probably not an issue that will be resolved soon.
- Dr. Bailey closed out the panel by noting that a lot is being learned. These studies are at their mid-point. He hopes to come back in two or three years to share additional findings.

VI. Administrative Business: August 26, 2016

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

Dr. Joseph Bocchini welcomed Committee members and other participants to the second day of the sixth meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and took roll. Voting members present were:

- Dr. Don Bailey
- Dr. Joseph Bocchini
- Dr. Mei Baker
- Dr. Jeff Brosco
- Dr. Fred Lorey
- Dr. Dieter Matern
- Dr. Stephen McDonough
- Ms. Annamarie Saarinen
- Dr. Beth Tarini
- Ms. Catherine Wicklund

Ex Officio members present were:

- Centers for Disease Control (CDC): Dr. Carla Cuthbert
- Food and Drug Administration (FDA): Dr. Kellie B. Kelm
- Health Resources and Services Administration (HRSA): Ms. Joan Scott
- National Institutes of Health (NIH): Dr. Melissa Parisi

Organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Robert Ostrander
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State & Territorial Health Officials (ASTHO): Dr. Christopher Kus (by phone)
- Department of Defense (DoD): Dr. Adam B. Kanis (by phone)
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes: Dr. Siobhan Dolan
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

VII. Newborn Screening Timeliness – Collaborative Improvement & Innovation Network (CoIIN)

Yvonne Kellar-Guenther, PhD
Evaluator, NewSTEPs 360
University of Colorado, School of Public Health

Dr. Kellar-Guenther's presentation focused on the work around the Collaborative Improvement & Innovation Network (CoIIN) for Newborn Screening Timeliness. The CoIIN was a 15-month un-funded project. Seven states participated: Arizona, California, Colorado/Wyoming, Iowa, New Hampshire, Tennessee, and Texas. An interdisciplinary approach was required and each state formed a team that includes a newborn screening laboratorian, a newborn screening follow-up person, and a hospital representative. The states learn together by sharing with each other the type of resources they used as well as successes and failures.

The CoIIN adopted the Committee's recommendations as their goals for improving timeliness from birth to reporting out newborn screening results.

1. Presumptive positive results for time-critical conditions should immediately be reported to the child's healthcare provider and no later than 5 days of life.
2. All presumptive positive results for time sensitive conditions should be reported to the healthcare provider as soon as possible but no later than 7 days of life.
3. All NBS results should be reported within 7 days of life (the "normal" screening results).

In order to achieve these goals the CoIIN used the following:

1. Initial NBS specimens should be collected in the appropriate time frame for the baby's condition but no later than 48 hours after birth, and
    a. Deviated from the Committee recommendations of no later than 24 hours as the recommendations came out a month after the data had been started
2. NBS specimens should be received at the laboratory as soon as possible; ideally within 24 hours of collection.

The CoIIN measured progress using the NewSTEPs quality improvement indicators by collecting monthly data, in aggregate, by state:

- QI-5a - Birth to specimen collection
- QI-5b - Specimen collection to receipt by lab
- QI-5c - Specimen receipt to reporting out of complete results
- QI-5d - Birth to reporting out complete results

The first indicator was specimen collection before 48 hours of life. Dr. Kellar-Guenther presented a graph that represented how the seven states did as a group. The graph was a median for each month of the percentage of dried blood spots that were collected within 48 hours of birth. In January of 2015, the specimen collection was 91.6 percent and by March of 2016, the group achieved the 95 percent benchmark. Two states were already at the 95 percent mark at the beginning of the timeframe. The other five states improved in the 15-month timeframe. As a group, the states met the goal.

One lesson was hospital reports. The barrier was that the hospitals do not know what they should aim for or how well they are doing. The solution was to provide hospital reports of how the hospital was doing in relation to other hospitals in the state. Another barrier was that the report cards were not being shared

with nursing or laboratory staff. Education was provided to hospitals about the value of sharing the report. Three states did surveys to hospitals to find out what the hospitals knew and understood. One state reported that only 36.2% nurses recalled watching the CLSI education video. To improve this, the state developed point-of-care educational messaging. Another barrier was state legislation. If the state says that the specimen must be collected within 48 hours the hospitals have a better reason to do exactly that.

The second indicator was that the specimen was received at the NBS lab within 48 hours of collection. The seven states in the beginning of the timeframe were at 68 percent and at the end were at 80 percent. One lesson learned what that education was a barrier in that the hospitals did not know what they should aim for. Providing hospital the reports did help. Another lessons learned was that the laboratories are only open 5 days a week to receive or process specimens. The solution was to increase the number of days the laboratory is open and processing specimens to 6 days a week

Dr. Kellar-Guenther pointed out to the Committee that one state laboratory is open 7 days a week, 24 hours a day, and that they are the only state at the 48 hour timepoint to actually be over that 95 percent benchmark that the CoIIN suggested. The specimens that were received within 24 hours are at 50 percent. She suggested that the 48-hour mark is potentially a benchmark that should be considered instead of 24 hours because this state is still at 100 percent for results reported within seven days of life, and 100 percent for critical results reported within five days. She suggested that this state is meeting the true end goal, even though they are not meeting this particular benchmark.

A final lesson learned about the second indicator is to decrease the time from hospital to laboratory that the specimens are with the courier service. Barriers include specimens spending too much time in transit, courier contracts not followed, and if a hospital is early on a courier route it cannot prepare specimens in time to meet 24 hour goal. Potential solutions include introducing or increasing courier system and meeting with the labs and the hospitals about what the hospitals could do about changing when they collect specimens, seeing if the courier could go back in the afternoon, or changing location of the pick-up, etc.

Another piece of the quality indicator was the results reported out within 3 days of lab receipt. Four states were able to provide information for this indicator. In January of 2015, the overall result for the four state laboratories was 25% and in March of 2016 the result was 57%. However, in the middle of the period, (August of 2015) the result was 77%.

Another challenge was the impact of adding new disorders. By testing for new conditions, one barrier was the need for different staffing. In some states, testing cannot be done in local labs before the FDA approves a test. It has to be done in the main State laboratory. Therefore, there was a delay in completing the report to the physician within 3 days of lab receipt.

Another lesson was between staffing and the workflow. In one example, a State had two primary times in the day that the couriers provided specimens to the lab. However, the staff was leaving for the day around the time the second specimens were coming into the lab. The State shifted the laboratory hours so that the staff had time to run the second set of specimens before the staff went home.

The last piece of the quality indicators was the results reported out within seven days of birth. Only two states were able to provide data. One state was above the goal line. The other state went from 9% to 32% over the course of the CoIIN. The barrier for this State was the inability to meet the goal in spite of education efforts and that the State was unable to provide courier service to all hospitals. The solution was to focus on reaching out to hospitals with the greatest percent of delayed specimens, regardless of size. The State also expand reach of courier service to help reach those “poor performer” hospitals.

All seven States were able to make progress with the CoIIN activities.

A new HRSA-funded project is NewSTEPs 360. Dr. Kellar-Guenther called this a CoIIN on steroids. This project is working with 20 states to achieve timely reporting of results in 95% of newborns who receive dried-blood spot (DBS) newborn screening within each state participating in NewSTEPs 360 by August 30, 2018. The awardees have received financial assistance and training on continuous quality improvements (CQI) techniques and coaching. They are sharing resources and are on monthly calls with the other awardees.

One example that has happened in Oklahoma with the NewSTEPs 360 CoIIN is the change in how often those hospital reports are sent by the State. By going from quarterly reports to monthly, this State now has a higher percentage of their hospitals having their specimens arrive within two days of collection. The State of Virginia has made a change in the time from collection to receipt by laboratory for six hospitals. The State of Wisconsin is focused on getting results into the hands of providers by the providers receiving faxes instead of the laboratory mailing the information to the providers.

NewSTEPs 360 is also working with Baby's First Test. This group conducted a focus group during the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) meeting with fourteen people representing eight states participated. One of the key findings from the focus group is that the heel prick (blood screening) has many steps and is only one part of NBS. Other finding include the observation that nurses are overwhelmed and do not receive updated training and dissemination of information/recommendations is difficult, especially making sure all staff (different shifts) understand or can implement changes is harder. Easy implementation means an easy win, so make the need for a specimen fit clearly in the workflow. The communication between staff, lab, and educators is key, but remember that turnover is huge barrier. The staff need to know why they are collecting the specimen, and how to do it, so bring newborn screening to a personal level.

Committee discussion

- Dr. McDonough complimented the presentation. He mentioned that in February 2015 the Committee encouraged states to have 95 percent to meet the objective of the test results, time critical in five days and all reports in seven days. He asked where HRSA was in this issue. Dr. Kellar-Guenther discussed the NewSTEPs Data Repository has 31 States that have MOUs and are entering data in it.
- Dr. Tarini asked what types of couriers were being used by the states. Dr. Kellar-Guether replied that state-run courier systems or FedEx were used by states participating in the CoIIN.
- Dr. Tarini asked if states could decide when the pickup comes and when the drop-off happens. Dr. Kellar-Guenther responded that she does not know how the contracts were negotiated, but it is easier to change a contract with a courier than it is to change the workforce.
- Dr. Brosco discussed that States may be adding new kinds of tests, particularly genetic and genomic sorts of tests, and it may be harder to meet the deadlines of five and seven days.
- Dr. Kellar-Guenther said that the group has not had to deal with that yet, but they do have a readiness tool to collect real-time data under the New Disorders grant to determine how long it really takes for new tests, and there is variation depending on the type of test. Right now she doesn't know, but requested they ask the question again in the future.
- Dr. Baker was able to comment because her state is experiencing this right now for the Cystic Fibrosis. In her state, they send the preliminary report to the doctor and tell them the Cystic Fibrosis mutation test is pending. They send another report once the Cystic Fibrosis mutation is available.
- Dr. Greene said that physicians would know that the test would tell them that the IRT was abnormal. If the CFTR is pending and the state laboratory is only doing CFTR sequencing on the top 4 percent, the physicians would know that the IRT was abnormal.
- Dr. Tarini thought that most physicians do not know the specifics of the tests.

In Michigan, the laboratory gave out the report for positive and presumptive positive, but they did not provide mutation data. The physicians did not know they could ask for the mutation data. In addition, when researchers surveyed primary care physicians, many of them got it wrong. She is suspicious that primary care physicians do not have enough understanding of the test, and would need to be notified.

- Ms. Saarinen thinks that States should do some explorations as to what a courier could mean as there are innovative new options available in the public sector. She suggested that there might be some new recommendations on how States use different kinds of couriers. She also said that a 24-hour benchmark seemed almost unachievable. She wondered about the standard and what may or may not change as a result of this newly funded work.
- Dr. Kellar-Guenther responded that the recommendation will not change. NewSTEPs will continue to collect data. She stated that meeting the five to seven day benchmark for reporting results was more important than the 24-hour metric.
- Dr. Tarini pointed out that the five to seven metric was defined by the committee and is an arbitrary metric. The committee should not be satisfied with this metric if it is possible to report results in four or three days.
- Dr. Bocchini stated that the timeliness workgroup decided they wanted to achieve seven day results with five days for time critical illnesses. Then they worked backwards to determine would be needed to achieve that. He does not think the committee is ready to change the recommendation.
- Ms. Bonhomme provided more information about the focus groups that were done with nurses as part of the CoIIN project. They targeted nurses who were shift leaders, or those who were responsible for bringing educational materials to the unit. No one had ever discussed newborn screening with the nurses or asked about their experience. The nurses felt empowered just having one focus group. Ms. Bonhomme stated that the collaborative structure of the CoIIN was important for engaging staff working on the front line with newborn screening.

Audience discussion

- Anne Comeau from Massachusetts thanked Dr. Kellar-Guenther for the presentation. It gave a peak at the complexity of the situation and nicely showed a variety of cooperative solutions. That said, when it comes to evaluation, she advocates for much less variety and very careful definitions of what the group is looking for. What is the benchmark for reporting a newborn screen? What is a newborn screening result? Should we also be looking at time-critical results and when those get reported out. She thinks we need to carefully define what they want newborn screening programs to aim for and encourages the committee to revisit the guidelines.

VIII. Robert Wood Johnson Project on Newborn Screening Timeliness

Beth Tarini, MD, MS, FAAP
Committee Member
University of Iowa
Amy Cochran, PhD
Research Assistant Professor
University of Michigan

Dr. Tarini's and Dr. Cochran's presentation focused on preliminary findings of a project from the Robert Wood Johnson Foundation on improving the efficiency of newborn screening from collection to test results in the state of Michigan. Dr. Tarini started her presentation by thanking her multidisciplinary team, which includes health researchers, an applied mathematician, a quality improvement expert, a healthcare

operations engineer, a newborn screening researcher and a health economist. She also thanked her advisory committee members on the project.

She discussed that newborn screening is a complex process. It requires coordinated and timely collaboration between multiple stakeholders that also is within and between clinical medicine and public health. There are different ways to organize and deliver NBS. Each state program designs its own process. Dr. Tarini was clear that different designs could be equally effective.

The project focused on three major steps of NBS process: the collection, the transport, and the processing of the specimen. The project also looked at what is happening within each step, including timing, staffing, frequency and availability. The goal of the NBS process, from birth to getting test results, is from five to seven days depending on the test. The rationale for the project is that by taking a broader perspective of the NBS process and performing a systematic analysis, the group could identify leverage points where they can potentially intervene and improve process efficiency.

The goal of the project was to use innovative dynamic simulation modeling techniques to systematically identify potential process improvement strategies for reducing time from collection to test results and then assess the trade-off between timeliness and cost for the strategies identified. A person will have an assessment of what is the incremental cost of changing the system (i.e. you should know what you are getting for what you are investing).

Dr. Tarini provided a brief overview of simulation modeling. It is a statistical method for identifying steps in a state's NBS process that can be modified to improve timeliness by running multiple simulations with data input. The implications are that it is a systematic and efficient method for assessing timeliness of a state's NBS process. It can identify steps in the process linked to significant change in timeliness (i.e., leverage points). It can be tailored to a state's specific process (i.e., state specific procedures and data).

Dr. Tarini discussed the early challenges and barriers to the project. NBS is a complex process. In Michigan there are 83 hospitals and each hospital potentially has 83 ways to collect a specimen. She talked about the variability in the organization and implementation at program and hospital level. The availability of data is difficult because not everyone is collecting the data that is useful for this model. She discussed what is the health outcome gain of less than 5 days from birth to getting the test results.

Dr. Tarini turned the presentation over to Dr. Cochran. Dr. Cochran focused on the data analysis of the project, particularly she concentrated on the part of the process that starts at birth and ends when the lab starts processing the specimen. The data was collected from the Michigan Newborn Screening Program from April 2014 to March 2015. There were 94,770 NBS specimens. Newborns from neonatal intensive care unit (NICU) or a special care unit were not included. The data also included several elements including hospital ID; time and date of birth, collection, and receipt of lab arrival; mileage from hospital to lab; and pickup schedules by hospital.

Dr. Cochran discussed the data. During the weekdays, births were more common than they were for weekends. Throughout the day, births were more common in the morning around 8:00am and then slowly declined until night. In Michigan, specimens are collected 24 hours from birth. That means that collections are going to be more common one day later. Dr. Cochran's data showed that specimen collections occur from Tuesday to Saturday.

For this project, she looked at the date from birth to collection and from collection to arrival at the lab. In Michigan, nearly 70 percent of specimens are collected within 24 to 26 hours. Over 99 percent of the specimens are collected within 36 hours. There is a greater variability in the times from collection to arrival at the lab. From the system's perspective, the project resources are going to be better spent in the collection to arrival at the lab time and trying to improve that because of the higher variability.

In Michigan, collections are picked up six days a week. Weekday pickups occur around 6 p.m. and hospitals have one pickup on either Saturday or Sunday. There is a fixed courier route. Couriers pick up specimens in multiple hospitals before they arrive at the lab.

Dr. Cochran wanted to understand where the variability comes in the collection to lab time. She did a linear regression to see what factors are important to collection to lab arrival. Hospital volume was not significant. She discovered that what was significant was the day of collection and the time of the collection. She found that in Michigan, the Tuesday collection is, on average, about twelve hours faster than a Saturday collection. The Friday collection is about three hours longer than a Saturday collection. Early morning collections are about three hours faster on average than the evening collection.

Dr. Cochran discussed that this is when simulation modeling comes into play. Could collection timing be important to NBS timeliness through its relation to lab hours and courier schedules? She used the previous data to create a realistic simulation to try to capture all parts of the system from birth to lab arrival.

Dr. Cochran simulated the following:

- Patterns of birth (including uncertainty)
- Birth to collection (including uncertainty) with tests ordered after 24 hours of birth
- Collection to pick up, allowing at least 4 hours of drying
- A fixed transit time of 10 hours
- Processing starts immediately during laboratory hours

By using this simulation, Dr. Cochran was able to explore what Michigan could implement before the state actually implemented it. She focused on what happens when you change the lab hours as well as what happens when you change the pickup schedules. By using this simulation Dr. Cochran was able to estimate a priori impact on timeliness. For example, she found that switching pickup schedules from 6:00pm to 9:00pm was estimated to have 12.6% fewer specimens received by the state laboratory 60 hours after birth.

Dr. Cochran turned the presentation back over to Dr. Tarini. Dr. Tarini discussed that this is the first step of the project of using the State of Michigan data to get a model and see how it actually works. The next step is to refine the model with additional data from surveys of other hospitals and state newborn screening programs. Another goal is to get data on the cost.

Mary Kleyn, the Michigan state epidemiologist and Lois Turbett, the newborn screening nurse coordinator participated in the discussion by phone and helped respond to questions.

Committee discussion

- Dr. Matern asked whether one should revisit the issue of when the sample is actually collected. In the NewSTEPs data, California is looking at 12 to 48 hours as collection. In Michigan, it is from 24 to 36 hours. He wanted to know if the simulation could model for 12 hours. And look at how the OBs are delivering the babies.
- Dr. Tarini said they could model that. She talked about a paper published in California that discussed what happens when you get those 12-hour specimens. Her understanding from the paper was you do not see a significant shift in the metabolic, but you do see an increase in the false positive rate of hormone-based tests.
- Dr. Matern mentioned that Dr. Piero Rinaldo is looking at this with CLIR and they are able to adjust by birth weight.

- Dr. Greene indicated that when you get those early specimen collections the CAH and Thyroid false positives go up dramatically. She wanted to know how much it would cost to do a simulation and could it be scaled to be used by people without a grant from the Robert Wood Johnson Foundation? And with other laboratories that sometimes introduce old-fashioned technology, she wanted to know if the hospital laboratory has to have control over all of the specimens. The laboratory can change its workflow within the laboratory, but what happens if the sample was never received in the hospital laboratory. What happens if it was picked up or accessioned on the floor?
- Dr. Tarini discussed health services research and the option to buy expertise of an individual who may have other expertise as well. Dr. Cochran works on the data remotely for Dr. Tarini. Therefore, Dr. Cochran does not have to be in Dr. Tarini's lab. Dr. Tarini is able to utilize Dr. Cochran's time and pay her for that time. Therefore, there are both an access issue and a cost issue that Dr. Tarini's thinks could be solved.
- Dr. Tarini inquired with Ms. Turbett if specimens go to the laboratory or are they accessioned on the floor in in Michigan hospitals?
- Ms. Turbett discussed that it is a mix. In some hospitals, the courier picks them up from the floor and those hospitals have their own way of keeping track of the specimens.
- Dr. Tarini responded that with regard to design, this is where it's the people on the ground all the way up to the 30,000 foot view of the modeler and understanding all of the processes in between. To the point about the costs, that is an important piece. Iowa did a cost analysis before this all happened. They went 7 days a week, 24 hours a day. The argument made to the public health department was in dollars only (i.e. not ability to have someone run the lab on a Sunday, or hire people, or to have them run it at night, etc), but in terms of dollars, it is on par potentially with adding a new disorder. Dr. Tarini highlighted that the committee does not explicitly discuss dollars spent when we add a disorder, but we consider dollars spent with regard to running a lab and timeliness. She indicated she wasn't saying this is right or wrong, but is pointing it out. If we are having dollar conversations about timeliness which affect all of the disorders, why are we not having those conversations about adding a disorder if those are comparable costs? One affects one disorder, and one affects 50.
- Dr. Bailey discussed that one of the key cost is getting the actual raw data to begin with and Michigan has a very good system to be able to do this, with time stamps essentially for when all these things happen. However, Dr. Bailey did not know if other states have that level of data. To him it seemed like the timing of stamps are the only way a researcher can actually do the modeling in any kind of cost-effective way.
- Dr. Tarini agreed and added you would have to track the specimens, more than just how many got here, but "X" percent arrived at this time.
- Dr. Bailey asked Dr. Cochran if there is a difference between mathematical modeling and simulation in what people would do in operation science? The models presented are very sophisticated, but operations researchers can take it and say, okay, now we have this system. For example, we've got 27 elevators going up and down in a large building. How do we program those elevators in a way to maximize efficiency?
- Dr. Cochran indicated she worked closely with an operations researcher on the model, who has a lot more expertise modeling the process steps.
- Ms. Keyln added that in her state they are lucky because the system is already designed to time stamp specimens. In terms of on the newborn screening card that means they know the birth date and time and the collection date and time. When specimen are received in the laboratory there are data coders who enter that into the LIMS system. For tracking the laboratory receipt, as soon as the card is scanned the date and time stamp is automatically added to the accession number, which is a unique identifier used to track the sample throughout the whole testing process in the

laboratory. So, all of our date time stamps were already routinely collected and tracked in the software.

- Dr. Tarini commented that not every state can do this now, but it's reasonable to consider the ability to aspire to it.
- Dr. Bailey commented that it is a good example of how that kind of data already exists.
- Dr. Bailey noted that the state lab doesn't really control what goes on at the hospital and the hospital doesn't really control what the courier does, etc, He described the benefits of a systems approach and how thinking about a whole system is different than modifying one piece.
- Dr. Tarini agreed. She also countered that we modify a whole system when we add a new disorder. So, it is not new to us to modify the system when it comes to certain things.
- Ms. Baker commented that she liked this because it is moving toward evidence-based decision-making. One question, other than modeling, can it become a template? Other states may have different data, for example different couriers coming in.
- Dr. Tarini responded that yes, the goal and the way this was posed to the RWJ was that this would build a process model, in the sense of a process model that can be manipulated in which different steps can go into it, input the data can be tweaked for the states, and that is the opportunity from the grants perspective to effect change. It's a tool that can be modified and used.
- Dr. Cochran also responded that yes, she thinks the next step could be taking this and turning it into some sort of app, where a different state could put in their own data and then model the whole process. She indicated this is beyond her expertise, but from her perspective it could be pretty straight forward and something that's normally done.

IX. Missouri's Experience Implementing Lysosomal Storage Disorders Screening and Follow-up for Pompe, Gaucher, Fabry and MPS-I and Krabbe Disorders

Sharmini Rogers, MBBS, MPH
Chief, Bureau of Genetics and Healthy Childhood
Missouri Department of Health and Senior Services

Dr. Roger's started her presentation by thanking the Missouri State lab, the follow-up staff and the four genetic centers. The goal of her presentation was to provide the legislative background, the process of implementation of screening for Lysomal Storage Disorders (LSD) in Missouri, screening results, how Missouri implemented short-term follow-up and the determining of the lab confirmatory results.

Missouri's legislation followed the same language as Illinois's legislation. The law was named after Brady Alan Cunningham who had infantile Krabbe. The legislation passed in August of 2009 and the state was mandated to begin screening by July 2012. The legislation specified that the Missouri newborn screening program would screen for Krabbe disease, Pompe disease, Gaucher disease, Niemann-Pick disease, and Fabry disease. The program also had the option to add other LSDs.

The state decided to use the digital microfluidics method. However, as the time came nearer to implementation the state discovered that they were not ready to screen for Krabbe, so contracts were developed with the Wadsworth Lab in New York to conduct Krabbe screening.

A task force was created in early 2012 to develop follow-up guidelines and reporting. New York began screening in August of 2012 and Missouri began the population-based pilot for Pompe, Gaucher, Fabry and MPS-1 in January of 2013. The intention was to begin screening for Krabbe in the State of Missouri in June of 2015.

Missouri has around 78,000 births annually and the lab screens about 92,000 samples per year (more samples are needed for repeats and unsatisfactory specimens). The average amount is about 375

specimens daily. The lab has two full-time employees dedicated to the screening for LSDs and one full-time employee for follow-up. Missouri has four contracted centers to provide the follow-up and confirmatory testing.

Dr. Roger's provided a schematic diagram of the workflow for screening using digital microfluidics. The testing takes about five hours. She provided the current referral cutoffs:

- GAA (Pompe) cutoff = ≤ 7.8 umol/L/hr (0.25% percentile)
- GBA (Gaucher) cutoff = ≤ 6.7 umol/L/hr (0.15% percentile)
- GLA (Fabry) cutoff = ≤ 7.4 umol/L/hr (0.52% percentile)
- IDUA (MPS1) cutoff = ≤ 1.4 umol/L/hr (0.07% percentile)

For three years, the lab has changed the cutoff several times. It is closely monitored by the lab with input from the task force and the genetic centers. Dr. Rogers discussed other aspects of establishing cutoffs. Enzyme activities drop slightly during the first 2 weeks of age and then stabilize after 14 days-of-age. Premature babies can have altered LSD enzyme levels and repeat screens are more reliable. Multiplexing with other enzyme assays helps assess reliability of sample results and risk for referral. Some seasonal variation is observed with enzyme activities, in that more carriers and pseudo-deficiencies will be detected during higher heat and humidity months. The lab was pleased with the performance of digital microfluidics as a screening method due to the ease at which it can be incorporated into the NBS laboratory and the ease at which it can be conducted.

Dr. Rogers next discussed screening for Krabbe disease. Between August of 2012 and July of 2015 Missouri sent samples to New York daily via overnight FedEx. New York tested the Missouri samples and retested anything less than 20 percent of the GALC mean. The DNA testing and LH GALC feed was performed if the first analysis was less than 12 percent. Missouri was notified for referrals if mutations were found. The samples and results were sent back to Missouri and referred to the genetic center.

New York screened 266,189 samples from Missouri for Krabbe from August of 2012 to July of 2015. New York reported 42 samples with polymorphisms; they were not referred for follow up because they were not at risk for Krabbe disease. New York reported 54 referrals and none were infantile Krabbe. They detected 6 genotypes of unknown significance, 3 genotypes of unknown onset and 42 with one known Krabbe mutation.

In April 2015, Missouri began validation for in-house screening for Krabbe using the fluorometric bench assay and molecular analysis for early detection. The screening was done in tandem with New York screening same samples. The lab requested 34 samples of previous Missouri positive Krabbe referrals, 4 with two mutations and 30 with one mutation. All samples were identified as normal except for one carrier of the Y303C mutation which happened to be slightly above the proposed cutoff. The lab also tested 29 previous Missouri polymorphs and those results were flagged as abnormal.

Dr. Rogers described short term follow-up in Missouri for Pompe, Gaucher, Fabry, Hurlet (MPS-1) and Krabbe diseases. See presentation for confirmatory testing and confirmed cases.

The State has contacted with four genetic centers to provide confirmatory testing and follow-up of infants identified by newborn screening. During the implementation phase, the lab did not provide results on the abnormal screens for the lysosomal storage disorders. The lab phoned and faxed the centers. The centers contacted the primary care provider to coordinate care with the family. At the completion of the implementation phase, LSD was fully adopted. The infant's family care physician was notified along with the centers of the negative result per the regular newborn screening protocol.

Dr. Rogers also discussed challenges with screening for LSD. The first major challenge is the number of referrals was larger than what was expected. Another challenge is finding a significant number of pseudodeficiencies, especially with MPS-1 increasing the patient's anxiety. There is a lack of medical management guidelines and practices for asymptomatic patients. She also discussed ethical dilemmas such as identifying carriers and diagnosing late onset conditions in the newborn period; potential loss of the parent/child bond when a diagnosis is made in infancy before signs and symptoms are present; inability to get life insurance, long term care insurance, and/or disability insurance; parents and patients do not "fit in" to the support groups. More information is provided in the presentation.

Overall Dr. Rogers felt that screening for the LSD's in Missouri is going smoothly. Incidences rates are at or higher than the published incidences and the false positive rates are similar to other NBS tests. No reported undetected cases have presented clinically as of August of 2016.

Committee discussion

- Dr. Matern discussed that it is sobering as a committee member that approves States testing for these conditions. After seeing what happens he sees that there are some potential harm. Dr. Matern thought this is mostly driven by false positives. He suggested that the Laboratory Standards workgroup look to define what a true positive is and see whether we can identify a means to reduce it. It is clear that the genotypes of uncertain variants are not helpful.
- Dr. Matern also disclosed a potential conflict of interest. He has a lab that can offer second tier testing for some of the conditions in Dr. Rogers's presentation. Dr. Matern's lab screens for three conditions for Kentucky: Krabbe disease, Pompe disease, and MPS-1. At six months, the lab had screened 25,000 babies. The first week of screening the lab identified one MPS-1 case. The second week the lab had a false positive for MPS-1. The lab has not had another one since, after addeding a second tier test for dermatan and heparan sulfate. The lab does not report anyone with low IDOA activity and normal glycosaminoglycans. Regarding Krabbe, the lab uses psychosine. Dr. Matern is surprised that the Committee does not talk about psychosine in relation to follow-up. He discussed that with respect to how useful psychosine measurements are in the follow-up of patients. He thinks any symptomatic patient with Krabbe disease at any age will have elevated psychosine, so it would be helpful to at least identify the early infantile cases in the newborn period, as there is a problem with late onset cases. He thought the Committee should consider whether the late onset are secondary targets. Regarding Pompe disease, Dr. Matern's lab is working on a second tier which he think if it works out will, it will be very easy for any lab to implement. Dr. Matern would like to help better define what the goal of the screening programs are.
- Ms. Bonhomme appreciated Dr. Rogers talking about where this puts families, in terms of it being a new experience (being identified with one of these conditions). She asked Dr. Rogers to talk a little more about what she indicated in the presentation about families not fitting into the established advocacy groups or support groups that are out there. Ms. Bonhomme also requested to hear a bit more about what Dr. Rogers heard in terms of what types of support families are given and what families are doing.
- Dr. Rogers has heard is that there are only a few babies that have been identified to have the infantile disease from the disorders that Missouri is screening for. The families are not brought together and therefore are not able to talk to each other. The Pompe support group and a Gaucher support group consist of people that were identified later in life. The infantile cases are families that feel like they do not fit.
- Dr. Parisi had a question about Fabry disease and the definition of carriers. She was struck by the fact that Missouri appeared to not have identified any female carriers of the condition even though this is an X-linked condition. She wanted to know how Dr. Rogers was defining a carrier, given the heterogeneity of those who do have symptoms.

- Dr. Rogers said that the centers send the diagnosis for females as Fabry disease and not as carriers. Dr. Rogers asked Ms. Atherton (a member from the audience) to discuss more about carriers.
- Ms. Atherton said that centers in Missouri do the follow-up for Fabry disease. Females that were identified as heterozygote for Fabry disease are classified as Fabry disease. She said that the lab is not going to pick up every heterozygote female through an enzyme screen for X-linked disorders. Therefore, there are probably a number of girls in the State of Missouri who are "carriers", meaning heterozygotes for Fabry disease. They have normal enzyme function and therefore were not picked up and referred through newborn screening.
- Dr. Greene asked if there is formal evaluation of the psychosocial impact on families.
- Dr. Rogers said Missouri had no formal evaluation.
- Dr. Greene wanted to know if Dr. Rogers has information about the experience of the clinical centers actually getting the testing done (i.e. what's the center's experience is getting insurance approval to see the neurologist, to have the spinal tap, to have the DNA testing done, to have the enzyme assays done).
- Dr Rogers said that in Missouri the centers do not have problems with Medicaid. As long as newborn screening is done for that particular disorder, they will approve all the tests. Tricare has had some problems with paying for certain tests. The state provided the centers some seed money to help if insurance did not cover testing.

X. Long Term Follow Up for Pompe Disease

Jennifer M. Kwon, MD, MPH, FAAN
Associate Professor, Neurology, Pediatrics, Pathology and Laboratory Medicine
Golisano Children's Hospital
University of Rochester

Dr. Kwon's presentation focused on the status of Long-term Clinical Follow-up Efforts

Newborn Screening for Pompe Disease.

Dr. Kwon noted she is not a Pompe expert, but she is a clinician with an interest in long-term clinical outcomes. Dr. Kwon wanted to thank Amy Brower (NBSTRN) and Mike Watson (ACMG) and Melissa Wasserstein and Priya Kishnani for their help with the slides and noted any views expressed in the presentation were her own.

Pompe disease was added to the Recommended Uniform Screening Panel (RUSP) in 2015. Even though newborn screening for Pompe disease was added to the RUSP to improve outcomes in those with infantile Pompe disease by allowing early initiation of treatment, screening is likely to identify more infants with late-onset Pompe disease (LOPD), anytime from early childhood to adulthood. Based on evidence review conducted for the Advisory Committee, it was predicted that annually there would be about 40 cases of infantile Pompe disease identified annually in the US and about 90 plus cases of LOPD.

NICHD supported pilot screening studies of Pompe in three states: Georgia, Wisconsin, and New York. NBSTRN also sponsors several activities. There have been several guidelines to come out from different organizations, for example ACMG (2006 and 2011) and Neurologist in 2012. Providers are seeing early-onset and late-onset cases. There are ongoing discussions taking place among providers who see Pompe disease NBS referrals: NBSTRN sponsored provider calls (began in June 2016), State-based provider calls, and Industry-sponsored (e.g. Genzyme) workshops. The discussions tend to be expert opinion driven and standardized approaches are evolving

Dr. Kwon presented a table describing the evaluations for monitoring of asymptomatic patients with Pompe disease and what long-term follow-up may look like. If anything is identified as part of this monitoring it could trigger consideration for treatment.

Dr. Kwon proposed questions we should be thinking about - how would a physician actually follow these late-onset cases? What do you tell families? At what point will a patient need to go on enzyme replacement therapy (which are every other week infusions), it is likely the treatment will continue for their lifetime. To that end, there are Pompe disease registries underway to collect data on clinical practice so we can look at these data and evaluate them. NBSTRN, individual states, and Genzyme are currently collecting data.

Recent questions that have been raised about late-onset Pompe disease (LOPD) Longterm Follow-up. How frequently should LOPD patients be followed? When isolated abnormalities arise, how should they be addressed (elevations in CK; complaints of fatigue, weakness, headache, pain; and minor or mild findings suggesting cardiac, pulmonary, or muscle involvement)? How much do we know about certain genotypes? For example, should those who are homozygous for the GAA splicing mutation, "-32-13T>G" have a simpler and less frequent follow-up regimen?

In thinking about when public health meets rare disease care and where things may go with regard to registries and Pompe disease, Dr. Kwon offered a newborn screening for Cystic Fibrosis (CF) as an example or model for them to use. Dr. Kwon attributed their success to ongoing evaluation of clinical outcomes using a centralized national registry, registry oversight by an advocacy organization committed to quality improvement, and access to steady sources of funding unheard of in other rare disorders screened in newborns.

In conclusion, Dr. Kwon described where the field is currently with regard to long-term follow-up of Pompe disease. There are some guidelines but clinicians are still not sure about certain aspects of how to follow and treat late-onset Pompe disease. There are Pompe disease newborn screening long-term follow-up registries being developed in pilot-screening states, with NBSTRN and with industry. There are ongoing efforts to clarify genotype-phenotype correlations using resources like ClinGen and to develop better biomarkers. The NBSTRN sponsored provider calls are a resource for clinicians grappling with immediate long-term follow-up questions.

Committee discussion

- Dr. Bocchini asked if Dr. Kwon could give an idea of how many providers are on the Newborn Screening Translational Research Network calls.
- Dr. Kwon said that the calls are not just for providers, as other newborn screening stakeholders also attend. She could not give Dr. Bocchini a specific number of the providers. She said that the stakeholders do talk to other.
- Dr. Brosco discussed that from the couple of presentations from the day, he can see certain ethics issues that will up from newborn screening that the Committee can anticipate. He, Dr. Aaron Goldenberg, and members of the NBSTRN group are putting together a paper that lays out the common ethics issues that come up for any candidate condition. He believes that it should be thought about before the condition get too far down to the evidence review workgroup. He hopes to share with the Committee at future meetings.
- Ms. Scott asked if Dr. Kwon knew if the CF registry is done only under informed consent. She wanted to know if it a patient-entered registry and data, or is it clinician-entered.
- Dr. Kwon said it is a clinician-entered registry program and all patients whose data is received have consented.

- Ms. Scott asked if Dr. Kwon had a sense about clinicians who are now seeing individuals with Pompe. She wanted to know if there are asking patients for informed consent around being part of that long-term follow-up database.
- Dr. Kwon said she would say yes. She made it clear that there are plans to develop a Pompe disease newborn screening long-term follow-up registry with NBSTRN. However, in order to make those plans a reality, some kind of way is needed to institute consents procedure. She also said that the Genzyme registry sites are already entering newborn screening data into the Genzyme active patient registry. They are doing this with the patient's consent. She says that there are still no way around the fact that this activity is an activity that requires patient consent.
- Ms. Scott said she thought that patients should give consent. She wanted an idea of whether or not the families who are being identified through newborn screening are being told of these registries and that they should participate. She believes that is the way to systematically collect the data.
- Dr. Kwon said that speaking for herself, she knows that the registry efforts are underway. She has two late onset follow-up patients that she follows. She has not presented the registry as an option yet because she think the registry process is still in the early days. She will encourage participation when she feels the workflow and the structure of registry oversight is clearer. She believes that all clinicians will be more than happy to enter data into a registry once it is improved.

XI. Workgroup Updates

A. Cost Analysis Workgroup Update

Alex Kemper, MD, MPH, MS
Condition Review Workgroup
Duke Clinical Research Institute and Department of Pediatrics

Dr. Kemper's presentation focused on methods for cost assessment of newborn screening expansion. He began by summarizing where the workgroup is with this work. The workgroup is focusing on two target conditions, MPS-1 and Pompe disease. The workgroup has been gathering estimates and ranges associated with the overall cost of screening. The first task was to gather cost data on various categories, such as equipment, consumables, laboratory expenses (maintenance, repairs, installation, update of information systems), labor, confirmatory testing and referrals, and indirect costs. Dr. Kemper pointed out that each newborn screening program organizes these costs differently, which contributes to variability. The workgroup developed a template to gather this information, focusing on the number of specimens evaluated by the program.

Dr. Kemper shared cost data reported by four newborn screening programs. He explained that costs can vary widely, depending on the screening platform used, the number of specimens tested annually, whether the program has a reagent rental agreement or has purchased equipment. In addition, some states did not report costs for personnel or overhead/indirect costs. There may also be cost associated with long-term follow-up and false positive results. All of these factors make it difficult to calculate the exact cost of newborn screening for a given condition. Other sources of variation include: a state's annual birth rates; the number of specimens per newborn; initial startup costs; funding source (federal vs. state).

Dr. Kemper also described the challenges associated with assessing costs, including limited time for collecting data and privacy issues. It may be possible to obtain cost data from vendors and researchers but it may not be representative of state public health newborn screening program.

The workgroup plans to develop a Cost Assessment Plan with the objective of determining the impact on the budget of a state newborn screening program. The primary data source will be state newborn screening programs. They hope to produce an estimate of the cost per specimen to add a condition. Dr. Kemper emphasized that the approach reflects traditional dried-blood spot screening in a centralized lab, not point-of-care newborn screening. The workgroup will finalize their methodology, submit a report and recommendations to the advisory Committee, and incorporate cost assessment into Condition Review procedures and timeline.

Committee Discussion

- Ms. Scott asked about the risks the committee should be aware of in considering cost analyses information.
- Dr. Kemper replied that the purpose of the cost analysis is to show what a newborn screening program might need to invest to screen for a new condition. It is often said that preventive interventions are cost saving. This is probably not the case for newborn screening because the conditions are rare and screening only benefits a small number of individuals. The cost analysis information will just be one piece of evidence that the advisory committee considers, and they should be cautious about how much significance it is given.
- Dr. Grosse also stated that the cost estimates are typically determined before there is an FDA approved test and it is difficult to say what the eventual cost to the states may be. The cost analysis does not include staff time associated with adding a condition or long-term follow-up.
- Dr. Bailey stated that the work done by the workgroup is important to ensure that the same approach is used to estimate the cost of any condition.
- Dr. Brosco stated that there may be conditions for which the cost analysis is more certain and that this would

B. Education and Training Workgroup Update

Cathy Wicklund, MS, CGC
Committee Member
Northwestern University

Please see the Power Point slides for a summary.

C. Follow-up and Treatment Workgroup Update

Stephen McDonough, MD
Committee Member

Please see the Power Point slides for a summary.

D. Laboratory Procedures and Standards Workgroup Update

Kellie Kelm, PhD Chair
Ex-Officio Committee Member

Food and Drug Administration

Please see the Power Point slides for a summary.

XII. New Business

There was no new business to discuss.

XIII. Adjournment