Advisory Committee on Heritable Disorders in Newborns and Children

Summary of Seventh Meeting

November 3-4, 2016

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) was convened for

its seventh meeting on Thursday, November 3, 2016 and adjourned on Friday, November 4, 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.
Distinguished Fellow
Early Childhood Development
RTI International

Mei Wang Baker, M.D.
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health

Joseph A. Bocchini, Jr., M.D.
(Committee Chairperson)
Professor and Chairman
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Louisiana State University

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Professor of Clinical Pediatrics
University of Miami School of Medicine

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Genetic Disease Screening Program
California Department of Public Health

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Retried Pediatrician

Dietrich Matern, M.D., Ph.D.
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Medical Genetics and Pediatrics
Mayo Clinic

Annamarie Saarinen
Co-founder, CEO
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Beth Tarini, M.D., M.S., F.A.A.P.
Associate Professor and Division Director
University of Michigan Health System

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

EX-OFFICIO MEMBERS

Agency for Healthcare Research and Quality
Kamila Mistry, Ph.D., M.P.H.
Senior Advisor
Child Health and Quality Improvement

Centers for Disease Control and Prevention
Coleen A. Boyle, Ph.D., M.S.
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Food and Drug Administration
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Chief, Cardio-Renal Diagnostic Devices Branch
Division of Chemistry and Toxicology Devices
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Health Resources and Services Administration
Michael Lu
Associate Administrator
Maternal and Child Health Bureau

National Institutes of Health
Catherine Y. Spong, M.D.
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DESIGNATED FEDERAL OFFICIAL
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Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

LIAISONS AND ORGANIZATIONAL REPRESENTATIVES

American Academy of Family Physicians
Robert Ostrander, M.D.
Valley View Family Practice

American Academy of Physicians
Robert Saul, MD
Medical Director, General Pediatrics
Children's Hospital, Greenville Health System

American College of Medical Genetics and Genomics
Michael S. Watson, Ph.D., F.A.C.M.G.
Executive Director

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Natasha F. Bonhomme
Vice President of Strategic Development

March of Dimes
Edward R.B. McCabe, MD, PhD
Senior Vice President & Medical Director

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

I. Table of Contents

I Administrative Business – November 3, 2016

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

A. Welcome and Roll Call

Dr. Joseph Bocchini welcomed Committee members and other participants to the seventh meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (Committee) and took roll. Dr. Bocchini introduced Dr. Robert Saul, who will now be representing the American Academy of Pediatrics. Voting members present were:

- Dr. Don Bailey
- Dr. Mei Baker
- Dr. Joseph Bocchini
- Dr. Jeff Brosco (2nd half of the day)
- Dr. Fred Lorey
- Dr. Dieter Matern
- Dr. Stephen McDonough
- Dr. Annamarie Saarinen
- Dr. Beth Tarini
- Ms. Catherine Wicklund
- Agency for Healthcare Research and Quality (AHRQ): Dr. Kamila Mistry
- Centers for Disease Control and Prevention (CDC): Dr. Coleen Boyle
- Food and Drug Administration (FDA): Dr. Kellie B. Kelm
- Health Resources and Services Administration (HRSA): Dr. Michael Lu
- National Institutes of Health: Dr. Melissa Paris (attending for Dr. Catherine Spong)
- Designated Federal Official: Ms. Debi Sarkar

Organizational Representatives present were:

- American Academy of Pediatrics: Dr. Robert Saul
- American Academy of Family Physicians (AAFP): Dr. Robert Ostrander
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- Association of Maternal & Child Health Programs (AMCHP): Dr. Kate Tullis
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Department of Defense (DOD): Dr. Adam Kanis
- Genetic Alliance: Natasha Bonhomme
- March of Dimes: Dr. Siobhan Doyle

- National Society of Genetic Counselors: Cate Walsh Vockley
- Society for Inherited Metabolic Disorders: Dr. Carol Greene

B. Opening Remarks

Due to technical problems, the minutes from the last meeting are not yet available. Members will be able to review it in time for the next meeting.

Nominations for new members of the workgroups are due by November 23. They will begin their terms in January 2017. Membership on the workgroups allows additional people to become involved in the committee's work. Workgroups will consist of committee members, organizational representatives, and outside experts. There will be approximately 20 people on each of the three workgroups. Each person will serve a four-year term. The terms will be staggered, to ensure continuity. The Chair thanked all workgroup members for their work and diligence during their terms. He asked that people continue to be active on workgroup projects in which they are involved until they are completed, even if the person's term has expired.

In 2017, the committee will meet four times:

- February 9 and 10 (webinar)
- May 11 and 12
- August 3 and 4
- November 8 and 9

Meeting dates have been set through 2020.

Ms. Debi Sarkar provided a standard reminder on the committee's advisory role and related ethics issues. She asked that committee members check with her or Dr. Bocchini before agreeing to media interviews. She reminded committee members that they must recuse themselves from issues on which they have conflicts of interest, unless they have received a special waiver.

II. State Statutes and Legislation Related to Coverage of Dietary Treatment of Disorders Identified Through Newborn Screening

Meg Comeau, MHA
Senior Project Director
Center for Advancing Health Policy and Practice
Co-Principal Investigator
The Catalyst Center

Ms. Comeau thanked her co-workers for their contributions to this project. She also thanked the committee members for their expertise and support.

She explained that the Catalyst Center has a cooperative agreement funded by the Division of Services for Children with Special Health Needs, Maternal and Child Health Bureau, HRSA. They provide technical assistance, conduct research and policy analysis, create resources and promote partnerships to improve the financing of health care and to promote access to care and health equity. Their primary audience are the Title V, child health care and children with special needs programs.

Last spring, they were engaged by the National Coordinating Center for the Genetic Service Collaboratives (NCC) to identify state statutes and regulations that govern the dietary treatment of disorders identified through newborn screening. She stressed that this was not intended to be an academic paper or original research. They also were not identifying shortcomings in treatment of identified disorders.

The intention was to identify the full range of funding resources. It was hoped that this would help parents, patients, and their providers to better find help.

The group consulted with clinical experts and consumer advocates about what to include in the updated document. They completed a comprehensive literature search on the topic of insurance coverage of medical foods. The original document was a chart of regulations and statutes by state. The updated document adds a new introduction, methods section, glossary, reference list and summary. This is intended to make the information in the chart more accessible to more users.

The full document was reviewed a second time by clinical experts and consumer advocates, and final edits made. The draft is being distributed to this committee.

They found that there are extensive state-to-state differences. Most states do have mandated coverage under insurance, as well as Children's Health Insurance Program (CHIP) coverage. However, the depth and breadth of what is available is highly variable between states and depending upon funding source. Two individuals in the same state with different coverage (Medicaid versus private insurance) could have very different services available. Six states limit their coverage specifically to foods required for children with phenylketonuria (PKU).

Thirty-five states have legislative mandates for coverage of medical foods for genetic inborn errors of metabolism, such as PKU, galactosemia and maple syrup urine disease Thirty-three states provide coverage of medical foods through their Title V/CSHCN or other programs. The language and vocabulary used in state statutes and legislation is highly variable and does not always conform to clinical norms.

Not every type of insurance programs are bound by state mandates. Self-funded and Employee Retirement Income Security Act (ERISA) plans are exempt. According to some statistics, 65% of employees are covered by some form of self-funded plan.

Next, the group will make any edits recommended by this committee. She asked that they be submitted in the next two to three weeks. Once the final report is designed and formatted in an easily understandable form, a dissemination plan will be created in

consultation with NCC and HRSA. She said that they hope to get the information out to as many people as possible.

A. Discussion

Dr. Bocchini said that the draft report was included in the briefing book.

Dr. Baker asked what category the newborn screening fee utilizing medical food would be placed. Ms. Comeau explained that the chart includes some information about funding sources, where that was available. Dr. Baker said that, for Wisconsin, the use of the state screening fee for medical foods is not noted in the chart.

In response to Dr. McDonough, Ms. Comeau explained that the current system is built on the existing funding system. There are many gaps and variability. This is an incredible challenge. She thinks that the national government could play an important role in closing these gaps and giving states incentives to provide more comprehensive coverage and services to meet the needs of this population.

Dr. Tarini asked if the report has any lessons learned, from a policy perspective, from attempts at the federal level. Ms. Comeau repeated that the federal government could play an important convening role. They could help to pull the disparate groups together who are providing services to the population at the state level. She stressed that this is a time of transition and flux, both in terms of the Presidential transition and unknowns about the future of health care reform nationally.

Dr. Watson said that a similar analysis was done in 2010 when Sen. Kerry was pursuing legislation in the Senate. He asked if much has changed since then. Ms. Comeau promised to look into that and to provide an answer to the committee. She will also look into anything that has been done to get Social Security coverage for more conditions.

Dr. Ostrander said his group is trying to pull together a coalition of organizations and special consumer groups, and this report will help. He asked if this table is just for children, or the entire population. He is especially interested in whether coverage for adults is included. Ms. Comeau said that the chart indicates when coverage is for all ages; however, the focus is upon children and young people aging into adult. She agreed that the field should be looking at these issues across the entire life course, and not just for children. She said that there is "something deeply discomfiting" about worrying about losing benefits after your 21st birthday.

Dr. Saul said that the AAP just published, in September, the Blueprint for Children. It outlines global goals, and how government agencies can make a difference. He encouraged Ms. Comeau to look at where the Blueprint helps to make a better case. He offered to take the Blueprint along with the table to various other parties in DC. Ms. Comeau said that the project is somewhat limited in being able to identify proposed legislation at the state levels. She liked the idea of "marrying" the two documents.

Ms. Comeau said that, once the document is finalized, the Catalyst Center communications team will design it into a format as usable and accessible as possible. They will then work with HRSA to create a dissemination plan. She hopes that the final document will be both technically comprehensive but also highly accessible by both experts and legislators. She hopes to hold a webinar, as well, to encourage more people to use the document in the field.

Ms. Bonhomme offered help in disseminating the final report.

Dr. Bocchini thanked Ms. Comeau for her presentation, and promised that the committee is interested in helping move the document forward. He asked committee members and organization representatives to submit their comments in the next couple of weeks.

III. Public Comment

A. Kim Tuminello & Heidi Wallis, Association for Creatine Deficiency: Retrospective studies on Guanidinoacetate methyltransferase (GAMT) deficiency; growth in the population of the GAMT community; prospective find of one GAMT child in Austria

Ms. Tuminello thanked the committee for her patient advocacy group to talk about GAMT. She said that many children have probably been undiagnosed. Their lifelong problems could be prevented with the provision of appropriate care. She said that at least three children have been found through newborn screening, and reminded the committee of their baseline of only one child for further work. She reminded the committee that many of their members have previously said it is a "no-brainer" that GAMT will be added in the future. She asked if it is appropriate to just keep waiting until "one more child" is found. This is position of waiting for someone else to find this deficiency, which is putting children's lives at risk. The lab can pick up GAMT. She respectfully asked the committee to add this dangerous disease to the Recommended Uniform Screening Panel (RUSP), especially since there is a safe, affordable treatment available.

Ms. Wallis talked about her family's experience with their daughter's GAMT, which was originally diagnosed as autism. She has regained speech now that she has gotten treatment diagnosis and treatment, but will always have mental deficiencies. In contrast, her brother was diagnosed at birth and received treatment five years earlier, and is completely normal. She said that she does not understand why the current testing results are inadequate to prove testing reliability. The studies already available "appear to prove to our community" that testing does work. She pointed to the child found in Austria as evidence that testing does work, even if it was done with urine rather than blood, as is done in the U.S. She said that there is evidence that the higher levels of creatine can be found in infant blood spots. She asked the committee to adjust the guidelines to include GAMT.

B. Kristen Stephenson: Developments in the regulatory and advocacy space regarding SMA and DMD nominations to the RUSP

Ms. Stephenson is a Vice President with the Muscular Dystrophy Association (MDA). She said that, in September, the MDA submitted spinal muscular atrophy (SMA) and duchenne muscular dystrophy (DMD) to be added to newborn screening. She said that a newborn screening program in Taiwan has found multiple cases of SMA, and a New York pilot has found a single child. This indicates that SMA is ripe to be added to RUSP. She said that her organization is partnering with others in efforts to get all newborns in the U.S. screened for this condition. Drugs are in the process of being approved to treat this disorder, and MDA is proud to be involved in these efforts.

Time is of the essence for adding these conditions to newborn screening and in starting treatment for affected children.

C. Kristin Lasko: Parent of a child with SMA type I offering comments on behalf of Cure SMA and the potential nomination of SMA to the RUSP

Ms. Lasko talked about her 3-year old son with SMA. She praised Cure SMA for helping her and many other families to get diagnoses and treatment for their children. Her son was diagnosed shortly after he turned two months, at which time she was told he only had a 50% chance of living beyond age two. The FDA's agreement for expedited consideration could soon mean a first-time medication to treat this condition. She said that, if he had been diagnosed in his first few weeks, her own son could have avoided hospitalizations in his first year. He could have received pre-symptomatic treatment that would have avoided further problems. Newborn screening will enable families to get treatment for their children as soon as possible.

Dr. Bocchini assured her that the committee "looks forward" to receiving the nomination package.

IV. Updates from the Condition Review Workgroup

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

Dr. Kemper said that the group has been charged to develop consumer-friendly guides. They have started by developing a template for these consumer summaries. Once they have developed the one on X-linked adrenoleukodystrophy (ALD), they will be putting it out for comment and input. These guides will also be used to help consumers and advocacy groups understand how the screening guidelines are developed and updated.

The guide will include an outline of what is being done throughout the country. They hope this will help the Committee when it is making recommendations.

A. Discussion

Dr. Tarini asked for an explanation of what is being prepared for the evidence review process. She would like to see something prepared for groups preparing nomination packages. Dr. Kemper said that they have developed materials to take as much of the mystery out of the process as they can. This includes material on how the Committee makes recommendations, and what kinds of things they take into consideration. They are hoping to have a web-based document on which someone can click on various steps and terminology to get more explanation of what it means and what will be happening at that stage. It will also provide assistance in how to fill out the various forms.

Dr. Greene is "very intrigued" with the review of the long-term follow-up activities. She said that there are "tricky" issues where long-term follow-up is defined in different ways across different sectors. Dr. Kemper said that they have to be careful about duplicating efforts others have already taken. He looks at it as coordination of efforts taken by various people after the point of diagnosis. He said it would be "nice" to conduct interviews with states and other stakeholders, but that can create problems in connection with funding sources. His group has submitted a list of areas in long-term follow-up to HRSA; once they have buy-in from them, they can pursue this further.

Dr. Tarini said that this has been a long-standing issue for the Education and Training Workgroup. She offered to speak with him about what they have learned in their efforts. Dr. Kemper thanked her, and said that his group has been working closely with Natasha.

Dr. Spong received confirmation that the group has been talking about this for a while. Dr. Kemper said that some work has been presented to the Committee in the past. His group has been working with the Genetic Alliance to improve the materials available to help people make recommendations.

Ms. Bonhomme said that they are working on both the graphic piece and the text to help the consumer users. Her organization is "happy" to help and get this out. She thinks they are closer than ever before in creating information to help families and advocacy groups which are pulling together the nominations.

V. Guanidinoacetate methyltransferase deficiency (GAMT) – Update from the Nomination and Prioritization Workgroup

Fred Lorey, PhD
Committee Member
Former Director, CA Genetic Disease Screening Program

Dr. Bocchini said that the nominating groups have submitted additional information for adding GAMT to newborn screening.

Dr. Lorey and the Committee's Nomination and Prioritization Workgroup reviewed e the initial nomination and the additional information; what GAMT is; and how it can be

treated. He noted that children who receive treatment early in life can maintain normal or near normal development. He also presented an overview of the research that has been done on GAMT newborn screening around the world so far. The largest program was in Austria, which screened over a million babies, and found no true positives. Other programs have had similar results.

The group has concluded that GAMT deficiency is a serious medical condition, and its natural history is well understood. However, only 110 patients are known worldwide. Dried bloodspots-based assays can be adopted for newborn screening (NBS) quickly and at very low cost. GAMT deficiency appears to be very rare, and the test sensitivity is very good.

The NBS assay is inexpensive and easily implemented. However, there is no FDA-approved NBS or diagnostic assay. He said that there is no agreed-upon treatment strategy, and metabolic control must be strict. No patient has ever been identified through NBS.

Going through the Committee's standard questions, GAMT does meet some of them. However, the last two questions of whether cases have been identified prospectively or if there are set treatment protocols cannot be answered positively at this point.

The recommendation to the Committee in August was not to initiate external evidence review for these reasons. The workgroup had recommended that proponents work with other experts to formalize treatment guidelines and to encourage continuation of NBS for GAMT deficiency in Utah and Australia, and to report as soon a patient has been identified prospectively. The consumer groups were invited to re-nominate the condition as soon as that happens.

New information has been submitted for Committee review. Information has surfaced of a child being identified with GAMT through NBS. The NBS found mild elevation of guanidinoacetate (GAA). The first follow-up urine sample had marginally elevated GAA levels. The second follow-up found normal GAA levels.

The case summary seems to indicate that the newborn was at low risk for GAMT deficiency, and was not followed up further. At six months, the child showed mild delay in motor and speech development. No diagnosis was made.

At 22 months, the child had a more complicated workup. The GAA levels in the urine sample were quite elevated and a lack of creatine and creatine phosphate was found in the brain. The Bodamer paper is silent on some details of findings, however. At that point, GAMT deficiency was confirmed.

The group has been trying to determine whether this case meets the "single case" guideline set at the Committee's August meeting. He said that it is unclear whether this case meet that guideline. He concluded that the system failed this child, since the diagnosis was not made based solely upon the newborn testing. He said that this case should be considered a false negative for the NBS system.

The workgroup concluded that this case is not a clean representation of early identification and diagnosis by the NBS system. They are concerned that too much is being done to make this case "fit". The question is whether another newborn test should have been used to better pick up this GAMT case.

As a result, the workgroup does not recommend that GAMT be referred to full evidence review at this time. The case does not meet the criteria of a single clear case detected by the NBS system. More detailed data on the NBS cutoff is needed and how it was arrived at would be helpful, as well as further exploration of the low and negative urine results.

The workgroup continues to recommend that the nominating group notify the Committee immediately when a true case is detected, diagnosed and treatment is initiated in time to improve the child's outcome.

A. Discussion

Dr. Bocchini opened the floor for discussion.

Dr. McDonough said that GAMT should not be a difficult decision. He said that the cost of screening is very low, as is the cost of treatment. He said that adding this condition to NBS should be a "no-brainer". He called upon the consumer advocates to continue their persistence.

Dr. Bailey said that he, too, believes GAMT should be referred for additional review. He said that there is enough evidence for that.

Dr. Matern said that he does not believe that the case identified in the 2009 paper would fall through the cracks today, due to improvements in NBS programs. The cost of adding this test to the screening are "minimal", with a very low false positive rate. They know what the mistakes were in the 2009 case, and can fix them going forward.

Dr. Brosco asked if the same problems would be present even if another case were to be found. He wanted to know if the failures in the 2009 case are idiosyncratic to GAMT, or with NBS overall. Dr. Lorey said that he, too, would like to know why the urine testing failed in that case, and what went wrong with the diagnostic testing.

Dr. Matern said that he believes the NBS results were mis-interpreted. He does not know if the later testing was done by the same people who did the newborn screening. There are many questions that are still unanswered as of right now. He said that the answers to these questions need to be found.

Ms. Saarinen said that she heard four or five unanswered questions during this presentation. The evidence review process is designed to find those answers. She thinks the overall evidence is "so strong", she can't believe that the Committee will not move ahead on this condition because of one thing. She thinks the nomination language needs some overhaul, in general.

Ms. Wicklund asked if anyone has asked Dr. Bodamer the outstanding questions. Dr. Matern replied that these are the kinds of things someone could verify in just a few weeks during the evidence review process.

Dr. Tarini said that the Committee should realize that the testing for GAMT is not idiosyncratic. She thinks it is a conflict to use this case as an example of the larger NBS system. She said that they cannot say that the case is meeting the system standard while also claiming the system is murky.

Dr. Kelm agreed with what Dr. Tarini said. She said that a piece is missing in terms of clinical validity. They cannot agree that strong sensitivity is present without knowing more about what the detected case. She is concerned about moving forward without the missing information about what happened in that case. She thinks the bar should be very high in adding conditions to NBS.

Dr. Baker noted that many babies have been tested without finding a single case. She wondered whether it is because the condition is so rare, or if there is something else at work. Dr. Matern responded that he believes it is a rare disease, which makes the ongoing pilot studies difficult. He believes the test is sensitive, and the problem is in the disease's rare occurrence.

Dr. Boyle said that the requirement for a single case is understandable for diseases that are more common. She would like to see better information obtained from Dr. Bodamer. That said, she does not see the Committee adjusting its standards every time there is a challenging situation.

Dr. Lorey said that the system failed the patient. However, not enough is known about how the system was set up to be sure the situation would not occur again.

Dr. Tanksley expressed concern that the Australian study has not detected a single case after over a million screenings.

Upon Dr. Tarini's request, Dr. Bocchini reviewed the three evidence-based core requirements for the Committee to consider: validation of the lab test; widely available confirmatory testing with a specific diagnostic test; and prospective population-based pilot studies. They have reaffirmed that the entire NBS system is effective by including a screen positive case within a routine or difficult screening program.

Dr. Matern said that the lack of a case found by the Australian screening program is more about the disease's rarity than the test's specificity and sensitivity.

Dr. Saul expressed concern that having too strict criteria could mean that they miss some things going forward.

Dr. Brosco noted that, in the 1950s and 1960s, they moved forward without criteria it "led us to trouble". On the other hand, the question here relied upon getting more information. He thinks it is worth finding out more about what happened.

Dr. Tarini said that, to be clear, in this case, the NBS did not identify a case. Further testing identified the case. The NBS deemed the child to be healthy, though.

Dr. Matern said that the group does not know how the Austrian system is set up, and whether the U.S. system would have done things right where that system failed. There is plenty of evidence that the follow-up review can uncover that there is little reason to believe this would happen again.

Ms. Saarinen sees this as an instance of the NBS finding a positive case. She noted that, in congenital heart disease, the initial test is confirmed with further testing. She thinks it is a disconnect to say there was a failure with NBS, when the failure actually occurred with the follow-up screening.

Dr. Tarini said from a logical standpoint, they are assuming the child would have been caught if the right confirmatory testing had been conducted. This can happen in any medical situation, but the fact remains that the case was not caught. In this instance, NBS did not identify a case.

Dr. Brosco said that this is exactly why evidence review would be so helpful at this point. If they had more information about this specific case, they could determine if the failure was in NBS, or something idiosyncratic in the NBS system itself.

Dr. Baker said that they clearly have a lot of confidence in this. She has trouble with the situation that they are not focusing just on facts. She wonders why this case was brought forward, since it does not prove the test's sensitivity. There are multiple good pilot studies going on, and they are trying to make this case fit.

Ms. Wicklund wondered whether it was appropriate to go to evidence review in order to get the questions answered. She wondered if there was some other avenue to get those answers.

Dr. Tarini said that there are two issues with evidence review. One is that the volume of work that would be required. It requires more than just a review of the literature; it requires a survey of the entire state for impact. If that is true, then they are going to have to pay for more work to be done in order to get a little bit more information.

Dr. Bocchini replied that the public impact is, indeed, part of the evidence review.

Dr. Tarini pointed out that Dr. Kemper can only do just so many evidence reviews. Thus, if this is sent in that direction, something else cannot be done. Dr. Bocchini said that the recommendation should be done on the merits of this condition, not in comparison to other work that can or cannot be done.

Dr. Matern repeated that the Committee does not know how the Austrian system operated at the time. There are four clinical diagnostic centers, and they do not know where the urine samples were sent. The evidence review would have to determine that, as well as the testing outcomes to see how good the diagnostic laboratories are at finding these cases.

Dr. Tarini stressed the fact that NBS did not find a case. She said that should be the only issue on the table remaining from last time the Committee considered this condition.

Dr. Bocchini said that the important thing to consider is whether the Bodamer paper and the circumstances surrounding that child's screen satisfy the Committee's criteria for going ahead with evidence review.

B. Vote

Dr. Lu moved that the Committee vote to move GAMT to evidence review. Dr. Bailey seconded that motion.

No one recorded a conflict of interest. Dr. Lorey abstained. The final vote was four votes in favor and nine votes against. The Committee did not approve that GAMT move into evidence review. Dr. Bocchini said that it appears to be very clear that the Committee wants to receive additional information as soon as possible that would help them to move into evidence review.

Voting in favor: Dr. Bailey; Dr. Brosco; Dr. Matern; Dr. McDonough; Ms. Saarinen.

Voting against: Dr. Baker; Dr. Bocchini; Dr. Boyle; Dr. Kelm; Dr. Lu; Dr. Mistry; Dr. Parisi; Dr. Tarini; Ms. Wicklund.

Abstaining: Dr. Lorey

VI. Adjournment for the Day

At this point, the Committee adjourned its main meeting. The workgroups met in separate webinars for their working sessions.

VII. Administrative Business – November 4, 2016

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

A. Welcome and Roll Call

Dr. Bocchini welcomed the participants to the meeting, and conducted the roll call.

Committee members in attendance:
Dr. Bailey
Dr. Baker
Dr. Bocchini
Dr. Boyle
Dr. Kelm
Dr. Lorey
Dr. Lu
Dr. McDonough
Dr. Mistry
Ms. Saarinen
Dr. Parisi
Dr. Tarini
Ms. Wicklund
DFO: Debi Sarkar

Roll call for organizational representatives was not provided.

VIII. Newborn Screening Surveillance Case Definitions

Marci Sontag, PhD
Newborn Screening Technical Assistance and Evaluation Program (NewSTEPS)
Colorado School of Public Health
Cynthia F. Hinton, PhD
NewSTEPS
Colorado School of Public Health

Dr. Bocchini said that, after the presentation, he wants input as to whether the Committee wants him to write a letter of support for moving ahead with the final stage of this project.

Dr. Sontag said that they anticipate submitting this manuscript to the MMWR in the coming weeks.

The case definitions for public health surveillance NBS were developed through expert workgroups, under the leadership of HRSA. Those were presented to this Committee in May and September 2012. This presentation updates that work.

NewSTEPS has incorporated these definitions into a national repository. They are also assisting states to develop systems for implementing the definitions for their own use.

Surveillance case definitions are intended to establish uniform criteria for disease reporting. They are looking at surveillance systems, and reporting positive results across systems. They are not intended to be used to establish clinical diagnoses or the standard of care necessary for a particular patient. They do not set guidelines for quality assurance, standards for reimbursement, or start public health actions. She presented an example using cystic fibrosis to demonstrate this.

She stressed that the NewSTEPS definitions are intended to ensure that all patients are considered in the same way for surveillance purposes, no matter what the clinical diagnoses may be depending upon how clinicians interpret test results.

The case definitions are intended to allow for monitoring of trends for reported conditions, detect unusual occurrence, and define a uniform population that allows for the evaluation of intervention and long-term follow-up for newborn screening.

The process for creating the case definitions began in June 2011, when HRSA convened gatherings of subject matter experts. She outlined how the groups operated to create the case definitions. From 2012 to 2014, various groups met to consider the various case definition issues.

The case definitions were sent to the HRSA Regional Collaboratives (RC) in 2012. That started another round of reviews, both for appropriateness and duplication. Throughout this process, the Committee has been updated with periodic briefings.

Other meetings have also considered the feasibility of incorporating these case definitions into NBS programs.

NewSTEPS piloted the definitions in ten states in 2013. Retrospective data for two years was collected for up to 10 cases per disorder. The definitions were then revised further based on user feedback to ensure clarity and uniformity across the definitions.

The final case definition tables for most of the initial RUSP conditions have been completed. They are available at the NewSTEPS website (www.newsteps.org).

Some conditions were not addressed initially, either because they are well-managed now (such as hearing) or they were added to the RUSP after the effort started. Workgroups for the new conditions are underway to finalize those case definitions. For another set of disorders, HRSA has contracted with a different group to create case definitions.

She presented an example of one of the case definition tables. She stressed that the case definitions are absolutely not intended to second guess clinical diagnoses. The tables are

not all-inclusive of every combination of what might be elevated; instead, they focus on what is most commonly seen in clinical practice.

NewSTEPS is now working to apply the case definitions in the state programs. The data repository is readily available to the state programs to allow them to evaluate their own programs and to determine what improvements might be needed.

Over 4,000 cases have been entered by 20 state NBS programs. This includes base demographic data, NBS processes, and case-specific information, which supports the case definitions.

She said that this is a culture shift for the state NBS programs. Thus, they have included toolkits and templates to help the state programs import their data into the repository. This avoids the need for additional data entry by the states. The toolkits include one and two page worksheets to help clinicians gather the required information.

A. Discussion

Dr. Bailey asked for clarifications about what the case definitions, and whether carrier status is adequately covered. Dr. Sontag said that this does not define a screen positive; that is defined by the NBS programs themselves. As for the carrier status, it is not uniformly done for all of the conditions. It is available for conditions where it is possible to identify a case versus a carrier. What the states do with this information is up to them, rather than a national decision.

The goal is to eventually have a national repository of all cases that meet the case definitions. Dr. Sontag said that they have a way to collect this information in a de-identified, anonymous manner. They are calling this collection a repository rather than a registry.

Dr. Greene asked about using MCAD as an example. She agreed with the basic case definition, but asked about the "problem of phase". Without further testing, the phase cannot be known if there are two mutations in different locations. Dr. Sontag said that there was a lot of discussion about this, and this is where they ended up. She offered to talk about the situation further.

Dr. Parisi expressed appreciation for the 3-year reviews built in the process. She said that, at some point in the future, NBS might be genetically based. She suggested that the case definitions have a caveat that, for most NBS programs, testing the parents is beyond the programs' scope at this time. Dr. Sontag agreed with this approach, noting that testing the parents would open the program to more disorders. Dr. Hinton said that, moving forward with the case definitions, they could set a goal for when to do an evaluation comparing the results with actual results. This information could be used to improve the definitions further.

Dr. Baker agreed with elements in the MCAD table.

Dr. Boyle asked if they have considered integrating this work into the oversight board. Dr. Hinton said that they have not considered that. Her group has looked at how the board re-evaluates things.

Dr. Tarini asked if this is part of a larger effort to have the states categorize and log all of their cases in an easily extractable manner. Dr. Sontag said that the beauty of these definitions is their utility at the local level. It helps the states better identify who might be true positives. It is a long-term process, and part of a larger effort at the state level.

Dr. Bocchini asked the Committee members for their input on whether the Committee or himself should be writing a letter in support of this project. A number of Committee members responded positively to that idea. The letter would go to CDC in support publication of the case definitions. Dr. Sontag said that MMWR asked her group to get just such a letter of support.

The caveat discussed today can be linked to the website with the case definitions.

IX. Workgroup Updates

A. Education and Training Workgroup

Catherine Wicklund, Chair
Beth Tarini, Co-chair

Ms. Wicklund said that the meeting the day before was "great". They received relevant updates from members, and talked about additional activities needed.

Last time, they were talking about creating a tool to help primary care providers with additional guidance for discussing positive NBS results that could be used along with the ACTion (ACT) sheet. Ms. Bonhomme is collaborating with ACMG on doing this. It is based on research done with Dr. Greene with research groups. They hope to have a draft document for Committee consideration at the February meeting. One major question is the underlying purpose of the worksheet. Ideas include not only supplementary information, but also things such as the psychosocial impact upon the family.

Dr. Tarini reported that Workgroup is exploring the potential to incorporate the supplemental content into other projects, such as the AAP resident education project; pediatric resident education curriculum from Yale; and existing American Board of Pediatrics Maintenance of Certification (MOC) projects. She said that she has received "some enthusiasm" from AAP on the importance of these issues; it is a matter of whether funding comes through.

The group's Educational Outreach Projects are looking to map where education resources exist, and then to find ways to disseminate them to appropriate audiences. Dr. Tarini said that "this is a huge, comprehensive undertaking", and there is a lack of funding to support the effort. "We have to find a way to do this on the cheap," she noted. Thus, they are

going to start to develop a matrix that identifies relevant stakeholders and the topics that would be important for them to know about NBS. Jeremy Penn presented an initial framework for discussion purposes; they will next submit it to State's working groups for more input.

Ms. Wicklund said that the workgroup has also been looking to leverage the Committee members and their professional organizations to help Ms. Bonhomme and the NBS Clearinghouse to determine the best way to reach genetic counselors. Ms. Bonhomme will put together a brief summary of the project for Committee members to disseminate to their own organizations.

The workgroup also wants to continue to focus on educating stakeholders on the importance of timeliness. They want to involve phlebotomists more on these issues. Ms. Wicklund said that the ACHNDC could consider inviting that group to address the Committee's next meeting.

The next NewSTEPS 360 meeting is in November. Ms. Wicklund said that a number of Committee members will be attending, and will put out feelers as to whether additional educational information really is needed on timeliness.

Discussion

Dr. Ostrander asked if they are looking to create one-size fits all educational materials, or several sets of information depending upon the severity of the test results. He also asked if the group has looked at materials already available. Dr. Tarini said that she has only done a cursory review, and found that the available materials tend to be focused upon cancer diagnosis discussions. Ms. Wicklund added that "we do not yet have a vision for what this will look like." A lot will depend upon the outcome of Ms. Bonhomme's work. She acknowledged that there is a "ton" of literature on communicating results and the impact upon families. The group is not looking to re-create the wheel; they are simply to make it easier for the people doing this. Dr. Tarini said that, if the ACT committee does not think this is needed, the workgroup will stop these efforts.

Ms. Saarinen also suggested that there is a lot of information already available on how to talk about disorders of sex orientation. Dr. Tarini agreed with her and promised to look at that information again.

Dr. Greene said that the Genetic Alliance has collected important information from families on these issues, such as the importance of acting quickly and how much to worry. She said that this information is on the Genetic Alliance website, in a way to help clinicians communicate. Dr. Tarini agreed with Dr. Greene's comments. She said that one problem with the ACT sheets is that they are very proscriptive. She thinks it would be very useful to bring the two groups together in order to meet more stakeholders' needs.

B. Follow-up and Treatment Workgroup

Stephen McDonough, MD, Chair

Dr. McDonough praised the new workgroup members, Dr. Brosco and Ms. Saarinen.

They are working to have a paper on medical foods to present at the February meeting. This sub-workgroup has had four phone call meetings. He reviewed the group's progress towards writing the white paper.

The workgroup is also working on quality measures. Dr. McDonough related their progress, as well. They are focusing on the domains of public health, clinical care and children/families. They hope to have a paper ready for the full Committee's consideration by next May.

C. Laboratory Standards and Procedures Workgroup

Kellie Kelm, PhD, Chair
Susan Tanksley, PhD, Co-chair

Dr. Kelm said that the meeting the day before was quite productive. She anticipates getting some "great candidates" for new workgroup members.

During the meeting the day before, Dr. Tanksley had made a presentation on strategies to reduce false positives, and Dr. Piero Rinaldo gave a presentation on what to do about false positives in NBS.

Dr. Kelm gave an overview of Dr. Tanksley's presentation. She mentioned the importance of having a common definition of what a false positive is. They also need to take into account how the testing is conducted and a number of other technical issues.

She also outlines the presentation on what to do about false positives in NBS. That one reviewed issues such as the use of second tier testing to prevent this problem. Dr. Rinaldo is hoping to raise an international call to action on these issues. There are a number of "dark side" elements of false positives, such as additional testing, medical and emergency room visits and admissions, specialists' referrals, and disruption to family life. Dr. Rinaldo had focused on the importance of keeping the false positive rate low, due to the high cost of following up each of these cases. They present a huge burden on the overall healthcare system. Dr. Rinaldo also gave an update on the R4S Project's status on these issues. R4S has a number of post-analytical tools for measuring this problem, and to improve detection of true positives. Over time, the rate of false positives has dropped somewhat, but is still just over three percent. Dr. Kelm also reviewed how the Collaborative Laboratory Integrated Reports uses big data within R4S to prevent false positives even further.

Discussion

Dr. McDonough asked what should be done to encourage public health labs to participate in the R4S efforts. Dr. Kelm discussed that a workgroup member had asked if these tools should be included in the systems manufacturers are making now. Dr. Rinaldo had said that some manufacturers do include this kind of tool. Dr. Kelm was not sure how to encourage public health labs to use that equipment.

Dr. Greene said that it is up to the states to "make decisions about their own populations". There may be a false positive, but another significant condition could be identified. As the false positive rate is decreased, she wants to know what is being done about the category of cases where something else potentially life-threatening is identified.

Dr. Tarini asked if special access needs to be provided to use R4S. Dr. Kelm said that the user needs to request access, and it is a user name/password system. Dr. Watson said that parts of the larger system could be limited to some users for research, but there is a level through which access can be obtained simply by providing data into the system. Dr. Rinaldo wants as much data as possible to be put into the system from NBS programs.

Scott Gross noted that the costs of false positives are "condition specific," and vary as to what is done in response to the false positive. He said that, in many cases, a positive is simply re-tested so that false positives are caught with a relatively minimal cost.

X. Future Topics

Dr. Bocchini asked if anyone had ideas for future topics.

Dr. Tarini suggested that the Committee review disorders already on the RUSP, to determine if they should stay there or be removed. This would complete the cycle of approval and surveillance. Dr. Bocchini said that this could be a good project for workgroups as they complete their current work.

Dr. McDonough asked when they can look at linking the birth certificate with the newborn screening.

Ms. Saarinen asked if there is any process in place to review the current NBS conditions, and if a separate workgroup could be set up to do that. She would like to review the evidence behind CCHD screening, similar to what happened with SCID. Dr. Bocchini agreed that this is a good suggestion. They should be looking at the implementation of each of the conditions the Committee has added to the RUSP.

Dr. Watson said that there is a broader area of concern, beyond metabolic foods, involving the cost of things at the federal level. Another area is genetic services not covered in NBS. He said that there are between 5,000 and 7,000 genetic diseases being examined in labs.

XI. Adjournment

Dr. Bocchini then adjourned the meeting. He thanked all participants for their involvement. He said that "it is clear" there is considerable work going on.

The next meeting will be a webinar on February 9 and 10, 2017.