U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

HEALTH RESOURCES AND SERVICES ADMINISTRATION
(HRSA)

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ADVISORY COMMITTEE ON HERITABLE DISORDERS
IN NEWBORNS AND CHILDREN

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MEETING

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THURSDAY
AUGUST 25, 2016

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The Advisory Committee met in the Terrace Level Conference Room, 3635 Fishers Lane, Rockville, Maryland, at 9:00 a.m., Dr. Joseph A. Bocchini, Jr., Chairperson, presiding.

MEMBERS PRESENT

JOSEPH A. BOCCHINI, JR., MD, Louisiana State University; Chairperson
DON BAILEY, PhD, MEd, RTI International
MEI WANG BAKER, MD, Wisconsin State Laboratory of Hygiene
JEFFREY P. BROSCO, MD, PhD, University of Miami
FRED LOREY, PhD, International Society of Neonatal Screening
STEPHEN MCDONOUGH, MD, Retired Pediatrician
DIETRICH MATERN, PhD, Mayo Clinic
ANNAMARIE SAARINEN, Newborn Foundation
BETH TARINI, MD, MS, FAAP, University of Iowa
CATHERINE A.L. WICKLUND, MS, CGC, Northwestern University

EX OFFICIO MEMBERS

CARLA CUTHBERT, PhD, FACMG, FCCMG, Centers for Disease Control and Prevention (CDC)
KELLIE B. KELM, PhD, Food and Drug Administration (FDA)
KAMILA B. MISTRY, PhD, MPH, Agency for Healthcare Research and Quality (AHRQ)
MELISSA PARISI, MD, National Institute of Child Health and Human Development(NICHD), National Institutes of Health (NIH)
JOAN SCOTT, MS, CGC, Health Resources and Services Administration (HRSA)

ALSO PRESENT

DEBI SARKAR, MPH, Designated Federal Official, HRSA
NATASHA BONHOMME, Genetic Alliance
MICHELE CAGGANA, ScD, FACMG, New York Department of Health Newborn Screening Program
DAVID DIMMOCK, MD, Rady Children's Hospital San Diego
SIOBHAN DOLAN, MD, MPH, March of Dimes
ROBERT GREEN, MD, MPH, Brigham and Women's Hospital
CAROL GREENE, Society for Inherited Metabolic Disorders
ADAM KANIS, MD, Department of Defense*
BARBARA KOENIG, PhD, University of California-San Francisco
CHRISTOPHER KUS, MD, Association of State and Territorial Health Officials*
ROBERT OSTRANDER, MD, American Academy of Family Physicians
CYNTHIA POWELL, MD, University of North Carolina-Chapel Hill
SCOTT SHONE, MD, New Jersey Department of Health Newborn Screening Laboratory
SUSAN TANKSLEY, PhD, Association of Public Health Laboratories
CATE VOCKLEY, National Society of Genetic Counselors
MICHAEL WATSON, MD, American College of Medical Genetics and Genomics (ACMG)

*via telephone

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P-R-O-C-E-E-D-I-N-G-S

9:01 a.m.

CHAIR BOCCHINI: Good morning. Welcome, everyone, to the August meeting of the Advisory Committee on Heritable Disorders in Newborns and Children. So we'd like to welcome all of you who are here as well as those of you who are on the line.

I guess the -- first I would like to introduce four new committee members who are here for their first meeting. I think many of them are well-known to you.

First is Mei Baker. Dr. Baker is currently the Co-Director of the Newborn Screening Laboratory at the Wisconsin State Laboratory of Hygiene as well as an associate professor at the University of Wisconsin School of Medicine and School of Public Health. She serves on the Newborn Screening Translational Research Network Newborn Screening Molecular Subcommittee and is a member of the Laboratory Standards and Procedures Subcommittee for our committee. Dr. Baker has

knowledge and experience in molecular genetics and biochemical genetics, and her fields of interest include the application of molecular technology in newborn screening; DNA-based and mass spec screening for genetic metabolic disorders in the newborn; and newborn screening for severe combined immune deficiency, as well as an interest in public health genetics.

Dr. Baker received her medical degree from the Anhui Medical University, People's Republic of China, completed her residency at the Anhui Provincial Hospital. Her training was completed in two different medical specialties, internal medicine and radiology. So we welcome you to the committee.

Next is Jeffrey Brosco. Jeff is an expert in history and bioethics. He practices general pediatrics and development behavioral pediatrics and leads an interdisciplinary team that assesses children with neurodevelopmental disorders such as autism and other intellectual disabilities. He has expertise and experience in

the Newborn Screening Program, the organization of healthcare services for children, and the education of professionals in family-centered interprofessional practice. Dr. Brosco currently serves as a consultant for Florida's Title V Children with Special Healthcare Needs programs. He currently is a professor of clinical pediatrics at the University of Miami Miller School of Medicine.

Dr. Brosco received his medical degree and doctorate degree from the University of Pennsylvania, completed his pediatric residency at the Jackson Memorial Hospital in Miami. So welcome, Jeff.

Next is Beth Tarini. Dr. Beth Tarini is the Fred G. Smith Chair in Academic Pediatrics and Division Director in General Pediatrics and Adolescent Medicine at University of Iowa. She is associate professor in the Stead Family Department of Pediatrics. Her research focuses on optimizing the use of genetic services in pediatrics. She is particularly interested in the organization and

delivery of healthcare services through population-based screening programs such as Newborn Screening. She also conducts research on parental medical decision-making and parent-provider communication about genetic testing.

Dr. Tarini received her medical degree from the Albert Einstein College of Medicine, completed her pediatric residency training at the University of Washington. She is a graduate of the Robert Wood Johnson Clinical Scholars Program at the University of Washington, where she received a Master of Science in Health Services. She also holds a Bachelor of Arts in Biology from Harvard University. So welcome, Beth.

And next is Annamarie Saarinen. Ms. Saarinen is a parent, advocate, and policy professional who has collaborated with leaders in the field of newborn and pediatric medicine, clinical research, public health, public policy, and technology innovation. She is co-founder and CEO of the Newborn Foundation Coalition, a

non-profit organization with the mission of leveraging technologies to improve health outcomes and access for newborns and infants. She has domestic and international experience convening experts in newborn screening, neonatal medicine, and maternal newborn and child health policy.

Ms. Saarinen is the mother of three children, including a daughter diagnosed with critical congenital heart disease and a brain tumor and a son with connective tissue disease. Her focus has been on health IT and medical technologies relative to early diagnosis and improved treatment infrastructure for newborn and pediatric care. Ms. Saarinen received her Master of Arts degree in Economics from Iowa State University and served as a public policy public fellow at the University of Minnesota Humphrey School of Public Affairs. So Annamarie, welcome to the committee.

Now we will take a roll call for the committee members and organizational representatives. So if you'll answer as here or

present: Don Bailey?

MEMBER BAILEY: Here.

CHAIR BOCCHINI: I am here. Mei Baker?

MEMBER BAKER: Here.

CHAIR BOCCHINI: Jeff Brosco?

MEMBER BROSCO: Here.

CHAIR BOCCHINI: Carla Cuthbert?

MEMBER CUTHBERT: Here.

CHAIR BOCCHINI: Kellie Kelm?

MEMBER KELM: Here.

CHAIR BOCCHINI: Fred Lorey?

MEMBER LOREY: Here.

CHAIR BOCCHINI: Dieter Matern?

MEMBER MATERN: Here.

CHAIR BOCCHINI: Steve McDonough?

MEMBER McDONOUGH: Here.

CHAIR BOCCHINI: Kamila Mistry?

MEMBER MISTRY: Here.

CHAIR BOCCHINI: Melissa Parisi?

MEMBER PARISI: Here.

CHAIR BOCCHINI: Annamarie Saarinen?

MEMBER SAARINEN: Here.

CHAIR BOCCHINI: Joan Scott?

MEMBER SCOTT: Here.

CHAIR BOCCHINI: Beth Tarini?

MEMBER TARINI: Here.

CHAIR BOCCHINI: Cathy Wicklund?

MEMBER WICKLUND: Here.

CHAIR BOCCHINI: And Debi Sarkar?

MS. SARKAR: Here.

CHAIR BOCCHINI: And then representing the American Academy of Family Physicians, Robert Ostrander?

DR. OSTRANDER: Here.

CHAIR BOCCHINI: American College of Medical Genetics, Michael Watson?

DR. WATSON: Here.

CHAIR BOCCHINI: American College of Obstetricians and Gynecologists, Joseph Biggio?

(No response.)

CHAIR BOCCHINI: Should be on the phone?

(No response.)

CHAIR BOCCHINI: Association of Public Health Laboratories, Susan Tanksley?

DR. TANKSLEY: Here.

CHAIR BOCCHINI: Association of State and Territorial Health Officials, Chris Kus, should be on the phone?

DR. KUS: Here.

CHAIR BOCCHINI: Thank you, Chris. Department of Defense, Adam Kanis, who is on the phone?

(No response.)

CHAIR BOCCHINI: Genetic Alliance, Natasha Bonhomme?

MS. BONHOMME: Here.

CHAIR BOCCHINI: March of Dimes, Siobhan Dolan?

DR. DOLAN: Here.

CHAIR BOCCHINI: National Society of Genetic Counselors, Cate Walsh Vockley?

MS. VOCKLEY: Here.

CHAIR BOCCHINI: And Society of Inherited Metabolic Disorders, Carol Greene?

(No response.)

CHAIR BOCCHINI: So that completes our roll call.

So now I want to go through some business. Okay. You're already ahead of me, as usual, keeping me on task.

Okay. So we have completed the roll call. Let's go next.

So one of the things that we have been looking at, as you know, we have set term limits and made some decisions about our organizational representatives. We are now in the process of completing the same process for our work group membership, and so these are what decisions were made about the transition of the work group members over time, and we have met with the leaders of each of the work groups and have come up with this organizational restructuring.

So for the three work groups that are in place for this committee, we are going to, based on trying to make the work group functional and have everybody be able to participate, on average, we're

going to try and keep the work groups to no more than 20 members. Each will have a four-year term limit, and then the chairs and co-chairs will now move forward to finalize term limits for current members and propose a timeline for members as they would roll off. Once that is settled, we are going to call for nominations for openings, beginning next month, and the membership of each work group will be finalized by January of next year.

The next item was nominations for committee membership in 2017. As you know, we will have additional members transition off this committee at the end of June, 2017. Nominations were due by May 16th. We received a record of 43 nominations, and we're in process for final decisions to move forward with the selection of the new members for next year.

So now just to refresh everybody's memory, we did establish a Timeliness Work Group to address issues related to timeliness of collection and processing of newborn specimens. The current charges to this work group were to

optimize successful strategies to address newborn screening, specimen collection, and transport; collection and dissemination of timeliness-specific practices from state newborn screening programs, including programs that have implemented efficiencies in collection, transport, screening, and follow-up; and to investigate strategies for improved standardization of communication for -- of newborn screening results to providers and families.

The -- this committee has worked quite effectively, and the rationale for having a role in timeliness is that, based on the reauthorization of our committee, this became part of our responsibility, to evaluate and follow and attempt to address issues related to timeliness. The -- go to the next slide?

The Timeliness Work Group has been very effective. They call themselves the 1.0 and 2.0 timeliness groups and have brought together a number of organizations as a result of the work of the timeliness group, but also multiple other

organizations. Considerable attention has been placed at the national, regional, and local level to addressing timeliness issues across the entire process for many states. Many QI projects have been completed, and I have listed here a number of the organizations that have been involved and have played a very significant role in improving timeliness, and clearly across the country, significant improvements have been realized.

So although it is important for our committee to continue to monitor timeliness activities and progress, we felt that with the -- we got input from the Timeliness Work Group that their work had been effective, and that it probably was time to consider whether the standing committees, or standing work groups, that exist within the advisory committee could take over this responsibility.

And I have accepted that recommendation, and so the Timeliness 2.0 Work Group will be dissolved. And I want to thank everybody who served on that committee, that work

group. That has been incredibly effective and very important to the newborn screening programs across the country. And ongoing activities related to timeliness will now be delegated to existing work groups within the advisory committee.

Now again, just as a reminder, these are the major projects that are ongoing within the three work groups of the advisory committee: Education and Training Work Group is working to create a companion piece to the ACT sheets that provides primary care providers with guidance and tips for discussing positive newborn screening results with parents, and educational outreach project, in collaboration with the Newborn Screening Clearinghouse and Baby's First Test.

Follow-Up and Treatment Work Group is looking at promoting the role of clinical quality measures to promote long-term follow-up and is working on a policy brief on the current state of medical foods coverage.

The Laboratory Standards and

Procedures Work Group is working to define and implement a mechanism for the periodic review and assessment of laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel to find and implement a mechanism for periodic review and assessment of infrastructure and services needed for effective and efficient screening of the conditions included in the uniform panel.

Next slide. So just as a reminder, the next meeting for the advisory committee will be held November 3rd and 4th. This will be a webinar meeting. You have the dates listed there of the 2017 meetings. And meetings have been set up all the way through 2020 so that they will become available to you so you can set them on your schedules.

So just an overview of this meeting: we will have a discussion and a vote related to one of the pilot study recommendations, which I will talk about in a little bit more detail momentarily. And this is related to the identification of one

positive screen and confirmation of a condition as part of the pilot study requirements.

Today, we are going to focus on sequencing, including panel discussion with newborn sequencing and genomic medicine and public health, the NSIGHT program. And tomorrow, we're going to hear updates on activities focused on newborn screening timeliness, Missouri's experience in implementing of LSD screening and follow-up activities, and an introduction to long-term follow-up for Pompe disease.

So now I would like to turn this over to Debi for some additional information.

MS. SARKAR: Good morning, everyone, and a very early morning to those of you listening in on the webcast who are on the West Coast and in Hawaii.

Thank you for joining us today. As usual, I have my standard reminders about ethics and conflict of interests. I want to remind the committee members that as a committee, we are advisory to the Secretary of Health and Human

Services and not to Congress. For anyone associated with the committee or due to your membership on the committee, if you receive inquiries about the committee, please let Dr. Bocchini and I know prior to committing to the interview.

I also want to remind committee members that you must recuse yourself from participation in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner, unless you are also an employee of the organization, or unless you have received a waiver from HHS authorizing you to participate. When a vote is scheduled or an activity is proposed and you have a question about a potential conflict of interest, please let me know immediately.

I also wanted to go over participation during meetings. So the advisory committee's legislative authority is found in the Newborn Screening Saves Lives Reauthorization Act of 2014. This legislation established the committee and

provides the duties and scope of the work for the committee. However, all committee activities are governed by the Federal Advisory Committee Act, which we call FACA, and that sets the standards for the establishment, utilization, and management of all federal advisory committees.

So according to FACA, all committee meetings are open to the public. If the public wish to participate in the discussion, the procedures for doing so are published in the Federal Register notice and/or announced at the opening of the meeting. For this August meeting, in the Federal Register notice, we said that there would be a public comment period, which we will have later today.

Only with the advance approval of the chair or DFO, public participants may question committee members or other presenters. Public participants may submit written statements, and also, public participants should be advised that committee members are given copies of all written statements submitted. And we do state this in the

FRN as well as the registration website. So just to reiterate, all written public comments are part of the official meeting record and are shared with the committee members. Any further public participation will be solely at the discretion of the chair or DFO.

And then just my usual reminder to everyone, please state your name to ensure proper recording of the committee's transcript and minutes. That is all I have.

CHAIR BOCCHINI: Thank you, Debi. So actually, before we look -- vote on the minutes of the prior meeting, I just want to recognize Dr. Howell in the audience. Rod is the initial chair of this committee and certainly has brought us, with his expertise, to where we are today, so glad you're here today, Dr. Howell.

(Applause.)

CHAIR BOCCHINI: So all of you received a copy of the minutes of the prior meeting, the May meeting, in your packet. Are there any additions or corrections to be made to the minutes as

distributed to the committee? Yes, oh, what's -- Dieter has one first, and then we'll go to --

MEMBER MATERN: I have nothing major. I sent mine already to Debi.

CHAIR BOCCHINI: Okay. All right. Susan?

DR. TANKSLEY: I sent some revisions to Debi as well. The biggest was I was present at the last meeting, so --

CHAIR BOCCHINI: Okay, we were missing -- okay, all right. Okay. Other than those, then let's -- we need a voice vote for approval of the minutes with the corrections submitted by Susan and Dieter to Debi. So we'll go alphabetical. Don Bailey?

MEMBER BAILEY: Approve.

CHAIR BOCCHINI: I approve. We're only going to ask the people who were here. Carla Cuthbert?

MEMBER CUTHBERT: Approve.

CHAIR BOCCHINI: Kellie --

MEMBER KELM: Approve.

CHAIR BOCCHINI: -- Kelm?

MEMBER KELM: Approve.

CHAIR BOCCHINI: Fred Lorey?

MEMBER LOREY: Approve.

CHAIR BOCCHINI: Dieter Matern?

MEMBER MATERN: Approve.

CHAIR BOCCHINI: Steve McDonough?

MEMBER MCDONOUGH: Approve.

CHAIR BOCCHINI: Kamila Mistry?

MEMBER MISTRY: Approve.

CHAIR BOCCHINI: Melissa Parisi?

MEMBER PARISI: Approve.

CHAIR BOCCHINI: Joan Scott?

MEMBER SCOTT: Approve.

CHAIR BOCCHINI: And Cathy Wicklund?

MEMBER WICKLUND: Approve.

CHAIR BOCCHINI: Thank you. So the minutes stand as approved.

So the next item on the agenda is the Pilot Study Work Group recommendation on required data elements, and I want to precede this discussion by reminding people that when the --

when Jeff Botkin presented the Pilot Study Work Group's recommendations, the committee, after discussion, accepted those recommendations, but there was some question raised about the one item specifically related to the finding of a single patient with a positive test that was confirmed to have the condition being tested for.

Subsequently, the draft of the policy statement was sent to the committee members, and again, committee members wanted to have -- some committee members raised a question about having additional information as to why that was an important component, and so we held the policy statement until this meeting so that we could provide additional information as to why the committee -- why the work group made that decision. So let's go through my slides here and just go kind of back over what happened.

So part of the major reason we decided to have the work group for pilot studies was that we wanted to see if we could standardize the information that is required by the advisory

committee to bring a condition forward for evidence review, and obviously, this is based on the fact that evidence review process is dependent on the quality data, and the pilot studies are essential to provide the evidence about several aspects in the newborn screening system.

And then the other component that made this important was with the reauthorization, the timeline changed, and that we have nine months from the time we decide to bring a condition to -- for evidence review for a decision to be made about whether to move that with an approval to the Secretary or to reject that proposal. So we wanted to see whether we could make sure that we had a strong process in place to provide the information necessary for the nomination to go forward. Next slide.

So the charge for the Pilot Study Work Group was to, number one, recognize and support current efforts regarding pilot studies and evaluation; identify other resources that could support pilot studies and evaluation; and identify

specifically the information required by the committee to move this nominated condition into evidence review process, so the minimum data required for a condition to be accepted for evidence review. Next slide.

So these were the recommendations. I won't go through all of them, but -- because they have all been approved by the committee. The one issue that we wanted to provide additional information about was item three, that data should be available from pilot studies involving population-based screening of identifiable newborns. Next slide.

And the key here is the recommendation 3(a), which is the study should be sufficiently large to identify at least one true positive clinically affected newborn for the condition under consideration. Next slide.

So Dr. Scott Shone was a member of this work group, and so we have asked him to make a presentation today on this specific issue to provide further information as to why the work

group made this decision and its importance. Dr. Scott Shone is the Program Manager for the Newborn Screening Laboratory at the New Jersey Department of Health. In 2008, he assumed this leadership role over the Newborn Screening Laboratory of New Jersey. He chairs the NYMAC, I guess your NYMAC Newborn Screening and Emergency Preparedness Work Group. He also serves as co-chair of the Steering Committee for the Association of Public Health Laboratories' Newborn Screening Technical Assistance and Evaluation Program, NewSTEPS.

So Scott, we appreciate you making this presentation, so we'll turn it over to you. Thanks.

DR. SHONE: Great, thanks. I want to thank Dr. Bocchini for asking me to speak today. As he said, I was on the Pilot Study Work Group, but I want to make it clear that not only am I going to try to share with everyone what the Pilot Study Work Group was considering, but also, once I was approached to speak today, I took the opportunity to speak to a great number of my colleagues in

newborn screening, state newborn screening programs around the country, and feel that while some of the finer points of the discussion are still not 100 percent agreed upon, the consensus is what I am going to present today, that this one case is necessary, and the reasons why, I will talk about them again, come from not only me, but my colleagues as well.

And so Dr. Bocchini did a wonderful job of covering my first three slides. I appreciate that. And we did talk about this, but I felt that I did want to highlight this and say that it is really under the leadership of Dr. Jeff Botkin, and it is humbling to follow his presentation in May, to now have to go over this.

But really, the Pilot Study Work Group was incredibly cognizant of the fact that we were just trying to identify the minimum necessary data to move a nominated condition to evidence review. We were not trying to reestablish the criteria upon which a condition should be reviewed for consideration of the RUSP, okay?

So it is easy at times to, in our discussions, slip to thinking about that process of evidence review, to RUSP, but I want to be clear that what I am going to talk about today, and what the Pilot Study Work Group really focused on, was moving a condition purely from nomination to evidence review so that robust review by the Evidence Review Work Group could take place, and then ultimately present the report to the committee here.

And as Dr. Botkin showed, the crux of the discussion from May focused around this one true positive. And I went back and I read the transcript. I don't know how many people read the transcripts of the committee meetings, but I did read the transcript because I wanted to get a real sense of what the concerns were to help try to address them today. And one of the things that stuck out to me in the transcript was somebody asked, what is one? Is it really more than zero and less than two?

(Laughter.)

DR. SHONE: And that might seem funny, and what I hope is to show today that, yes, with respect to positive integers, one is more than zero and less than two, but with respect to nominations of a condition and consideration for evidence review, it means a great deal more.

So this is the process by which new disorders get added to the Nationally Recommended Uniform Screening Panel, right? Conditions are nominated, they get moved to evidence review, which is the process that we're talking about here. There is an evidence review process that is in place, that is standardized, provides data out through a matrix, and then the committee decides on the disorders for recommendation to the RUSP, to the Secretary of Health and Human Services.

And the purpose of this process is to identify conditions that have great public health significance for which it is imperative that four million newborns each year be screened, that the federal government will recommend that states implement screening for these conditions. And

through that process, identify data that shows clearly and in a robust fashion that there is benefit to performing this screening and that, again, clearly, the benefits outweigh any of the harms associated with mandating screening across the country, right?

If we break that down into processes, Dr. Bocchini said that now evidence review by law must take place within nine months, right? Historically, this process could take -- I don't want to say indefinitely, but could take a great deal of time. And so it is imperative at this point to truly identify, what are the sufficient data to allow for a thorough and robust review such that the Evidence Review Work Group can provide a report back to this committee, and upon which you can decide, is that data, are those data, robust enough to warrant recommending the entire country of newborns be screened for a disorder, right?

So not only is there an imperative weight based on what we're talking about here, a country of newborns, but we now have to do this in

a much more truncated fashion. So it is important that the data in demonstrates that the Evidence Review Work Group is going to be able to effectively accomplish their task. And I am sorry. I know we have seen this jellybean diagram a lot. It made its debut around timeliness. I want to thank Susan for bringing it to the world, I suppose.

But -- and we used it to great success around timeliness. It was easy to focus on the lab test, and how to make the lab test more efficient and faster. But once we got down and discussed the process, we realized that there is a whole host of pre-analytic, analytic, and post-analytic steps that need to be reviewed and improved with respect to getting critical results back, okay? NYMAC, Dr. Bocchini mentioned on the NYMAC, we just held -- we are in the process and are about to complete holding an entire webinar series this summer that covered the entire system.

When we are considering new disorders, it is no different. Simply talking about is there a lab test, is there a test, does it work,

trivializes the fact that there needs to be a system in place to identify children, diagnose them, and ultimately get them into treatment in an expedient manner. The identification of one newborn in a pilot study on some level shows that this system can exist.

So at the last meeting and since, there has been great discussion of why can't we just go back and grab a retrospective specimen? Isn't that sufficient to show that this works? And the answer really is no. Identification of retrospective specimens is not real-time. What newborn screening programs do on a daily basis is real-time, and this committee laid down recommendations recently with respect to timeliness, that all time-critical disorders are reported out within five days of life, and the entire Newborn Screening Panel is reported out in seven days of life. That is real-time. That is what we deal with on an everyday basis.

That includes collection of the sample, transport of the sample, receipt, accessioning,

testing, reporting results, and getting that child to diagnostic testing, ultimately diagnosed, and then treated. Simply pulling a specimen from a child who was diagnosed with symptoms merely provides data for analytic validity. It demonstrates the test works. It ignores the rest of the entire process. I have the screen in front of you.

It is a crucial part of the recommendations that the Pilot Study Work Group proposed. I believe it was Recommendation 1. You have to have a test that shows analytic validity. But it does not demonstrate that there is a process in place that a child who is picked up through that analytically valid test will ultimately be diagnosed.

Now the data we have on new disorders prior to newborn screening is based on individuals who are diagnosed with symptoms, and we're all aware that once newborn screening is initiated, the natural history of all these disorders dramatically changes, right? That is the goal.

That is why we have that process I talked about, adding disorders to the RUSP, right?

With respect to SCID, we went into SCID assuming, or thinking, that there would be about 1 in 80,000 babies or so, give or take, that would be identified with SCID. New Jersey implemented SCID just over two years ago. We have screened about 200,000 babies. We have already had four confirmed classic cases of SCID, two leaky SCID, and a host of other lymphopenias, well more than we ever expected, right?

And I would say that with newborn screening, on new disorders we have, that is often the case. We find well more than we ever anticipated. If a pilot study fails to demonstrate even the basic level of incidence you expect, much less zero, we must pause and think, one, is the data upon which we're basing our review and our assumptions accurate? That it calls into question everything upon which you are basing that movement forward.

More importantly, what if the data is

right and the system is not working? The system is not set up to identify these children. Then screening them and throwing them into a system that is not ready to either diagnose them or treat them is a failure, and it is dangerous. And so identifying at least one in a pilot study shows that there is evidence upon which the Evidence Review Work Group can base their report.

This is one of my favorite quotes, and I use this often in my lab: in God we trust, all others must bring data. W. Edwards Deming has many quotes, if you Google him, around quality and process. He also said, if you can't describe what you're doing as a process, you don't know what you're doing.

And everything we're doing is based on data, moving from nomination to evidence review to recommendation for the RUSP, and ultimately, the acceptance or not by the Secretary, relies on robust data. If any of the data is missing, it creates uncertainty, right? We must have numerators in addition to denominators.

Otherwise, upon which can we base any calculations, upon which can we actually consider our conclusions valid?

I'm going to talk a little bit about diagnosis because I mentioned the process earlier. Diagnosis is part of that process. Diagnostic tests are developed to look at a group of symptomatic individuals and identify which of the symptomatic individuals actually have disease, right? But I talked about us changing the complete natural history of this process. We are now adding a whole host of asymptomatic individuals, screen-positive asymptomatic individuals who are now in a group with symptomatic individuals.

We know that we can identify the symptomatic individuals by the diagnostic test. That has been proven. But can this diagnostic test also identify the asymptomatic individuals that belong in that group? And that's a big if.

If we think about cystic fibrosis, we all know that at times, the diagnostic tests for cystic fibrosis, sweat testing, can come up with

a false negative, right? The good news is that is not common, but it is possible. If we think about cystic fibrosis and our entire view of that was based on an elevated immunoreactive trypsinogen, and maybe we have DNA to show that, on a molecular level, the baby should have cystic fibrosis, but every time we did sweat testing -- or the only data we had showed that negative sweat testing, we would have to pause and say should we be screening all these babies for CF, because ultimately, we can't diagnose them, right?

Dr. Bodamer published a paper on GMT, and I don't want to make this about GMT, but in 2009, a baby was identified through routine newborn screening, but the urinary GA levels were normal, right? So the screening test worked for that child, but the system failed. So what good is that? If we don't have a system in place, we have failed that child, and not having a case in a pilot study that is screen-positive and ultimately diagnosed must cause us to pause.

At the last meeting, someone posed the

question -- or it actually wasn't a question, it was a statement, that when we're considering the lives of newborns, we can't be beholden to process. And I would say the fact that we are considering the lives of newborns, we must be beholden to process. It is imperative that the committee's process be uniform.

The criteria upon which every disorder is evaluated by the committee could potentially vary, but the process must be uniform. Now historically, the process has varied. But it doesn't mean that from this point forward, the committee can't decide every disorder proposed to this committee through nomination will be treated the same, subjected to the same criteria, because otherwise, you're setting up a moving target, and it is not fair to the system, especially the people nominating new conditions, if the target is not clear. What do they need to meet?

More importantly, a lack of uniformity in the process endangers the validity of the process itself. It makes the process look

haphazard. And again, these decisions that the committee makes impact four million babies each year, and I am not saying that you don't realize that, believe me. I say that with all due respect. But there is a danger of looking haphazard with the impact of the decisions.

But ultimately, so what? My other favorite thing: so what? When we go to hospitals and train them on why newborn screening is important, we say so what? And we explain to them, give examples of how babies from their hospital were impacted. Here is an MCAT baby that came out because you collected at 25 hours of life and got us a sample by day three of life, we reported by day four of life and saved this MCAT baby's life. But so what about this?

What if a pilot study doesn't have a case, and we just go to evidence review? All right, you have nine months now for evidence review. Some have suggested that is just simply a risk the committee is taking that a case will show up in the next nine months. The problem is risk

is a measure of uncertainty, and as I said earlier, there is -- you're lacking data. So how can you measure your uncertainty? It is not risk we're talking about, it is pure uncertainty.

The only way to address uncertainty is through research. That is the goal of the pilot study. So the committee must decide what level of uncertainty are they willing to accept? And if it is a great deal of uncertainty, does that mean implicitly that research is acceptable?

So in essence, what is one? I go back to the question from last meeting, what is one? Yes, it is a positive integer more than zero and less than two. But it is data. It is data that permits some level of analysis. One does not mean that a disorder is ready for the RUSP. It does not mean that the evidence review process does not need to take place. It simply means that the evidence review process can take place.

The robust standards that the committee has established for evidence review need to be maintained. Again, at the beginning, I said the

Pilot Study Work Group was not looking to change evidence review. We were simply trying to define nomination to evidence review.

One shows on some level that the entire newborn screening process could work to identify newborns, again, versus retrospective samples, which simply provide analytic validity. It supports some level of post-newborn-screening incidence review that look at natural history: what could we perhaps see? One demonstrates that diagnostic process can actually identify a true case from all the asymptomatic screen positives. Again, the system works, not just the test.

And finally, one creates uniformity that we so desperately need for this process, a standardized procedure. It is the minimum number of true positive newborns identified in a prospective pilot study needed to demonstrate that data exists from the newborn screening system to support moving a nominated condition to evidence review.

And so I look forward to a robust

discussion, but before I hand it back to Dr. Bocchini, I need to thank the Pilot Study Work Group. It was a privilege to work with all of them. I learned a great deal. I continue to learn a great deal from my colleagues, my colleagues in other state programs, who helped brainstorm on this topic and helped me put the presentation together. And finally, I greatly appreciate the time that you have given me to present the ideas to you, and I am always open and available for questions. Thank you.

CHAIR BOCCHINI: Scott, thank you very much. We appreciate the work you put into putting this together. Thank you.

This is open for discussion now. Fred?

MEMBER LOREY: I just wanted to say thanks, Scott. You hit the nail right on the head.

CHAIR BOCCHINI: Beth?

MEMBER TARINI: I also want to say that was excellent. That was very clear and reminds us that we are not just engaged in looking at the biochemical piece, but this is entrenched in a

process. Obviously, I am biased since I am a health services researcher. And if the process doesn't work -- if the survey system doesn't work, you don't deliver the health outcomes you intended to deliver.

I am fully aware that you are not intending to change the evidence review process. Can you go back to the slide, the last slide? And I -- but I think you inadvertently raise an issue that I think the committee needs to sort of address, and I think it's an elephant in the room, as I've sat on this as a liaison to this committee and watched the discussions, which is if the presence of one case is important because -- and I think that this is true, I agree with you because it demonstrates how the process works and how it can actually identify a case, then by that argument, the evidence review seems to suggest that the evidence review should consider how that process took place, and right now, we have not really looked at that.

I call back the -- I think it was the

MPS 1 case, where we didn't really look into -- you know, we had the data on I think it was Missouri, like what happened, these cases were identified, but we didn't really look at the process, we just know they were identified. We didn't really dig deep into the outcomes of the kids and what the process showed.

So I think when this comes up and we talk about this is a demonstration, finding one case, of how the process has worked, it sort of raises the issue of do we have to assess that process as part of the evidence review? Although I know that is not what your intention is, it sort of does raise I think this issue that we have not dug deep into before.

MEMBER MISTRY: This is just a follow-up to Beth. I mean, do you mean before the evidence review or as part of the evidence review?

MEMBER TARINI: Oh --

MEMBER MISTRY: I think that's important.

MEMBER TARINI: -- I think part of,

yes, as part of.

MEMBER MISTRY: Okay.

MEMBER MCDONOUGH: I have a few comments here. Our decision last meeting not to advance guanidinoacetate methyltransferase GAMT deficiency, the evidence review was an unfortunate decision, but it was described as a no-brainer by several. A very rare disorder with low cost of screening, little false negatives, and inexpensive treatment did not go on to further study.

There is no doubt in my mind that GAMT will eventually be approved, be it in two years, five, or ten. Until then, how many children with GAMT will go undetected and suffer intellectual disability, speech development limited to a few words, and recurrent seizures?

During the GAMT discussion, there was statements we need to be consistent and retain credibility, and that was SCID, the committee delayed approval for one year to get one case. How many children's lives were worth that one year's delay?

The incidence of SCID is between 1 in 40,000 and 75,000 births, which means up to 60 to 100 babies are born in the United States every year with a fatal disease by age two. Without newborn screening, many are not diagnosed until late. And how many children died of SCID from that one year delay?

In retrospect, SCID should have been improved in 2009 without requirement to get that one positive. The screening test was good, the condition serious, and effective treatment was available. We need to learn from our previous decisions and modify our approach. Requiring one positive does not appear to be scientifically valid. Approving SCID in 2009 would have been reasonable based on the science, and all that showed, that a year later, that the case was there, and the decision we could have made in 2009.

During yesterday's orientation, we were asked not to get caught up in the emotion of advocates, and it is ironic that today, we are asking to vote on the committee's emotion feeling

comfortable with a requirement of one positive. We do not need to further add unnecessary barriers to newborn screening such as the requirement for one positive to be detected for evidence review.

CHAIR BOCCHINI: Well Steve, thank you for your comments. I think that we need to separate individual decisions about particular conditions from the process within which we identify what is necessary to make that decision, and so I think that the -- this is not specifically related to what we discussed in terms of making the decision about GAMT or SCID.

I think the issue that was raised by the pilot committee, the pilot study committee, and the laboratorians is what is necessary to make sure that the test will work in a laboratory setting that would then enable it to be effective to take care of children? I think you have two examples, one of which with SCID that we now have the evidence that it is very effective. But before we had that, we didn't have that evidence, and so it is very difficult to say that the decision should have been

made before we had a single positive test.

It goes back to what I said at the meeting, is that you're in a position where you would make a decision about whether to add something to the RUSP without ever identifying a single case before we made that decision through the Newborn Screening Program, and I think that is the key issue here, is that the laboratorians need that evidence to prove that the test is effective, but as Scott said, that is only part of the process, but specifically about the test that is being used, it is important to make sure that that test works, and so that is the issue here. That key criteria, the work group indicated that it was supported, that, and I think the committee supported that, but was asking for additional understanding of why that was the case, and so that is where we are.

So Cathy?

MEMBER WICKLUND: So I was -- thank you. That was a great presentation. I appreciate it, and yesterday, we did hear Ned talk more, and I thought that was excellent as well, so I

appreciate that as well.

And I was the one who had a few questions about this, and I do think that this was really helpful to kind of go through it again, and I think Beth has a good point about the process. I think I was looking at it more of a, like, you identify a case and that is proving analytical validity, and that was kind of where I was at, as opposed to the broader picture that you brought forward, so I appreciate that.

I also think it is hard to -- we don't know the harm -- and I guess Steven I am kind of like addressing a little bit of what you brought up, we don't know what the harms are in implementing a test that we don't know if it works, and I think that is what is really hard to measure. So I appreciate the -- you know, nobody wants babies to die. Nobody wants, you know, this to happen, but I think when we frame it that way, it almost feels like no matter what, we have to -- my voice is shaking -- no matter what, we have to approve everything, and I think that is really dangerous

territory to go into.

MEMBER BROSCO: So a quick comment, and then a question about procedure.

It was -- thank you, Steven, for your comments. And I think that one of the things that is easy to do from history is to point to examples where we should have moved forward and would have saved some people. It is also relatively easy to find examples where we move forward without thinking and probably shouldn't have. And so he said anemia is one example where we screened millions of babies thinking that it was like another PKU, and it turned out to be a benign condition.

It is hard to show real harms. There are some children who were treated and probably didn't do well, but they were not really measured. So you can sort of go back and forth on that. So I think you're right, Cathy, we can't just base it on that.

I guess my question about procedure is if we did choose to say that we can move forward

without a single case, and the nine months' time clock started, and a case did not come up, and our Condition Review Work Group said look, there is really not a lot of evidence, but here is what we have, are our options at that point -- and this is a procedure question, is it just yes or no? Or is there a well it looks pretty good, we can hold on? So just what exactly does happen at that point if a case does not come up?

CHAIR BOCCHINI: Well, go ahead, Joan, do you want to address that?

MEMBER SCOTT: Based on the legislation, the committee would have to vote because -- and if the -- would have to vote at that nine months.

And the other thing to take into consideration is we ask a lot of the evidence review process. They are looking at not just the evidence around the test and the system. There is the public health impact analysis, there is the cost analysis that is going to be added on, so that is not a trivial thing to do in nine months. And so,

you know, I would be concerned about putting something forward in the hopes that within that nine months, there was going to be that case found that then the committee would be able -- would have enough information to be able to make a decision on, but the committee would have to vote at the end of nine months.

MEMBER BROSCO: And just to clarify, that vote is yes or no?

MS. SARKAR: This is Debi. Even -- we have never encountered a situation like that before, but I think just based on previous votes, even if the vote is no, the committee can provide -- can ask the work group to go back to look at more evidence, or it could be seen as a pause, or if the committee decides, the nomination might start over again. This is -- we have not gone over this territory, but I do think there are options.

MEMBER LOREY: I remember the first ALD vote, I think it was, we voted no because Dieter's work was not done yet, but in the letter that Joe wrote, it said something like we realize there is

data, and we can reconsider.

CHAIR BOCCHINI: For providing very specific data, then we were waiting for that to move forward, right.

MEMBER MATERN: Dieter Matern. So I think -- thanks, Scott, again, for your perspective, but what we're talking about is really Recommendation 3, which talks about the true positive. And then the discussion kind of went off about diagnostic processes after the screening is done. And I don't think we have to talk about it because Recommendation 2 already talks about the diagnosis and that the -- how -- what the clinical intervention, et cetera, are, with the patient identified.

I wonder whether we are struggling about the definition of what the goal of the disease definition actually is that we're screening, because going back to in the past again starting screening for PKU, the idea was you find only patients with PKU and not the hyperphenylalaninemia for other reasons.

One could have made a specific definition that you only look for severe phenylalanine hydroxylase deficiency. And so going forward, maybe we have to be more careful, and the proponents have to be more careful, that they define what disease we're actually screening and making sure that, yes, if we use a biochemical marker, there's a high likelihood that you find something else that you didn't intend to find, and those we have processes to have primary targets and secondary targets and deal with all of that.

So I would say that we have to make sure going forward that we define things that we want to do. The issue with the true positive and the analytical process is -- and we discussed it last time a little bit, does it really have to be prospective, a new case, or could it be a true positive sample that has been collected previously and is now added blindly into the pilot study, and would you pick that case up?

And again, that would be most likely a classic case for the disease, which is usually the

first goal of the screening. So I think there are issues that we have to see whether we can allow them in specific scenarios, but I think again we can build a process around it, we just have to be clear about it.

And it -- sorry -- because, as Jeff said yesterday, the easy work is already done. Now, we deal with the rare and ultra-rare diseases. And to find those prospectively is very difficult, not to speak of the issues of consenting for a pilot study if you want to do it prospectively and openly.

CHAIR BOCCHINI: So you're not arguing against the need for a positive, you're just talking about the possibility that you could achieve that in various different ways?

MEMBER MATERN: If it's about --

CHAIR BOCCHINI: Yes.

MEMBER MATERN: -- testing that the assay works, you don't have to have necessarily a sample from the --- yeah.

CHAIR BOCCHINI: Okay. All right. So we have Beth and then Don.

MEMBER BAILEY: So thanks very much for the good presentation, Scott, and I think you laid out very clearly a lot of the concerns that the state labs would have as well as, of course, our committee. You know, we definitely want to be recommending things that are feasible, and we definitely want to make sure that we have the right evidence to make a really good decision.

I think it's a little -- just a couple of editorial comments. I think it's a little unfortunate that we're being pushed by the time, the nine month, you know, timeline of legislation, and the -- looking down being the only choice. That forces us into making some decisions that might not be the ones we would make if we weren't operating under those constraints.

So, given that, I think we just have to recognize several things. One is I think we're setting a very high bar for conditions to move forward to evidence review, and it will slow down the process. That may be appropriate and may be what our committee needs to do, but it will -- it

does create a higher bar.

There is no natural funding source for this type of pilot, for pilots that are done before a condition is recommended for the RUSP, and so, you know, this will have to be pulled together from a variety of sources, and Dieter made a good point about we are going to have to anticipate that these will almost certainly in the future have to be done under a consent model, and when that is the case, you don't really have true population screening, you have screening from a subset of people who agree to this.

So I think we have -- you know, I am not saying that I am opposed to it, but I'd just say, this, it's much more complicated than was presented, and we're being -- and it is going to make it very difficult for new conditions to actually provide the data that is needed to help satisfy this request.

CHAIR BOCCHINI: Scott, do you have a comment?

DR. SHONE: I'd just like to respond to

Dr. Bailey's last comment about -- regarding the RUSP.

You know, initially, I talked about what I perceive, and I think what the Policy Work Group perceived, as that process for the RUSP is that the data exists prior to addition to the RUSP. It is incredibly dangerous to suggest adding a condition to the RUSP to justify getting data outside of the consent model that we now fall under.

I mean, I agree 100 percent that the legislative impacts of not only the changes to the Common Rule and changes to this timeline have profound impacts, and we have to work under that system, but I would -- it is -- in my view, the purpose of the committee adding disorders to the RUSP is not to gather data for a condition, it is there is data to support a condition.

And I would also just say that I understand, I agree 100 percent, the easy work is done, and it is hard to say. I mean, Cathy said it best, which is nobody wants newborns to suffer or die. I am a parent as well. I am lucky that

they are healthy, but I want to see my healthy and grow up healthy as well.

That being said, there are huge impacts to these decisions, and just because there is a test available does not mean that everybody should be subjected to that test.

MEMBER BAILEY: Right. So just to clarify, I was not suggesting that --

DR. SHONE: Okay.

MEMBER BAILEY: -- that we use the RUSP as a mechanism to then justify further studies.

CHAIR BOCCHINI: All right. And I think other than the first 29 conditions, okay, we're going to get to -- other than the first 29 conditions, which were added based on a consensus of the expert group, I don't think this committee has added or considered adding something to the RUSP without pilot study data. So it has always been pilot study data has been part of the requirement for adding something to the RUSP.

So we got Beth, and then Mei. Okay.

MEMBER TARINI: So two comments. One

is I think the committee has to consider -- that we have to consider the -- there seems to be this presumption that we will find a case, it is just a matter of time, which may be true. Maybe if we go in with zero, that eventually, and even if in that nine-month period it doesn't occur, that there will be a case.

I am not so sure. I don't know. The others who are deeper into the science can speak to how certain we will be given the background data we have. The piece, though, that comes up then is we go into it with -- we go into the assessment of finding one case with the bounds, like Dr. Caggana just said, of knowing well, it is about -- I'll make it up, a 1 in 50,000 estimate of case prevalence, but that is based -- largely often it is based on prior population-based screening, and we know from multiple other examples in medicine that when we screen, we find often different prevalences.

So what would happen if we go in and there are zero? We think it is going to be much more common than it is, and it turns out that it

is rare, or it could be the opposite, it could turn out to be more prevalent. So we do have this uncertain -- this other layer of uncertainty going on about what is the prevalence which has an -- I think an impact on the value of the screening.

And then the second piece is to --

MEMBER BAILEY: Excuse me, but couldn't that be answered through retrospective studies, the prevalence question?

MEMBER TARINI: No.

MEMBER BAILEY: No?

MEMBER TARINI: No. No, because you have not -- unless you have screened everyone in the population and you have -- and you can find -- I say no unless you have the ability to screen everyone in the population, you have the ability to use a diagnostic test to confirm that screen, and here is where the problem with the healthcare system currently stands, you have health outcomes data on them, and that is where you go off the chasm of I can't tell you if that child's blood spot from 20 years ago that is positive means that they are

healthy today or they have symptoms, or that -- I can tell you probably if they're alive or dead. That's about all I can tell you based on the population-based data we have. But I can't tell you anything more then, if they have mild symptoms that are misattributed to something else, if they have no symptoms, or if they truly have the disease. That is where the retrospective data falls apart. It is this overdiagnosis and/or misdiagnosis -- I am not saying it is all overdiagnosis. It could be mis-.

It could be we think they have no disease, and in fact, they do, it has just been misattributed by a physician or by themselves to something else. That is the law I think, or the shortcoming, of the retrospective. You do not have a thorough, final assessment of health.

But -- and my -- the second point I just want to bring up is on the harms comment that Dr. Brosco made is we -- and I don't know the histidinemia literature very well, but I do know this, having worked on this specific element of the

field about harms and unintended consequences of newborn screening, is that if -- that oftentimes, we have not measured it, and as one of my mentors said, if you don't measure it, you won't find it. And if you didn't find it, but you didn't measure it, it doesn't mean it didn't exist.

And so again I am not saying that there are significant harms of every test we do or that those harms justify not screening for a particular test, I am saying we just don't know, often because we have not looked, and we have not qualified them, and we have not quantified them. So that creates a bit of a problem when we talk about harms. We are dealing with an uncertainty that we have not really sort of looked at.

CHAIR BOCCHINI: Mei, and then Mike.

MEMBER BAKER: Hello? Okay. I just want to add on one thing. We -- I read the Recommendation 3 as a beyond-level-3 test, because we all know newborn screening tests, we set the threshold when we do screening. And I think a prospective study, the value sometimes cannot

replace by, you know, the identified, or this kind of situation.

The reason is that you set this ratio, and you have the test definition, what you want to find it, and you don't know in the real situation what you get. We already talked about the PKU hyperphe anemia, so let's give it a chance. If you find the case, or maybe you don't find a true case, you find some minor situation, keep the opportunity to assess it. I think this is valuable data for going forward.

DR. WATSON: You've got quite a problem. The entire process is completely unlinked, I think, if you look at the fact that NICHD funds a pilot based on some prediction of incidence, and you don't get to the number, or you don't find your positive in that amount that has been funded for the pilot, then you have a -- it is not going to be easy to get more money quickly.

So I -- you know, you're going to end up with the states mandating something that becomes more apparent to them, and that is where you're

going to generate more data, so it sort of defeats your purpose of trying to make a recommendation before the mandates happen. So I think you're probably going to have to step back and look at the entire process right from how you fund pilots because it -- you are not going to be guaranteed of getting that true positive in that funding period.

So, you know, I think you have a huge sort of policy problem about how all of these pieces come together to do these big multi-state pilots. We are doing three of them right now, and they are all -- I mean, because of OHRP, they are all sort of predicated on your having recommended them already before the implementation pilot is done to generate good performance data on the test. So I mean, it is quite a mess, frankly.

DR. OSTRANDER: So I -- okay. Bob Ostrander, American Academy of Family Physicians. I am going to sort of I think restate what Dieter said.

Everywhere else in medicine, when we

are dealing with things that are hard to detect or rare processes, we always prefer a prospective blinded study before we take action. Sometimes we can't do that, and we don't wait to take action if we can get to a reasonable retrospective study. It is not as good, and we need to recognize that, but it seems to me after hearing this whole discussion about rare diseases, and Dieter's comment about using, you know, some blinded blood spots, that one could do a retrospective study and get a reasonable degree of certainty without finding a case by putting it through the process that is going to be used going forward to get that piece of information.

Is the test effective? Can the diagnosis be confirmed? What's the false positive rate in a general population of blood spots that we have stored? And get a reasonable retrospective certainty that doesn't require a positive case being detected going forward.

Now, you have to recognize the potential pitfalls there. It is not as good, just

like anywhere else in medicine, it is not as good as a prospective study. So you need to do more thinking about the other issues. And for instance, you know, Beth talks about the unlooked-for undetected harms. They are going to be easier to find in a prospective study. They are going to be harder to find or impossible to find in a retrospective study, so then another piece of the analysis, and whether that happens in the pilot study stage or in the review process, another step in that analysis is trying to make a reasonable assessment of what the harms might be, realizing it's not going to be as good.

But for certain conditions, the potential harms are likely to be fairly low, and those could be put forward. I think we need to have an Alex Kemper grid for those kind of -- you know, for that kind of thing, if we're going to allow a retrospective approach. But it certainly seems now that we're into the high-hanging fruit instead of low-hanging fruit, that we should be looking at the whole process.

The other last comment I am going to make is -- and I agree with Scott, I mean, we can't leave the process out, but if we're dealing with rare things, I think the process needs to be in that pilot study section, the pre-evidence review, especially with the fact that we have a legislatively mandated, not scientifically mandated, time frame, that the process feasibility piece and cost piece should be studied and assessed in parallel, and only if you pass the process piece in a retrospective study piece and a reasonable consideration of the potential pitfalls of using retrospective studies would you push it on to evidence review, but I think confining yourself to prospective studies with rare conditions does not fit anything else we do in medicine.

DR. GREENE: So, first I wanted to put something into the record with respect to harm, and staying away from psychological harm, and staying away from the whole pitfall of questions of possible harm with some of the current proposals. Going back in history, there was screening for

neuroblastoma. It was thought to be a wonderful thing to identify the neuroblastoma early, using urine, finding the catechols, and the same thing happened as with other newborn screening that the frequency was higher than was expected, and lives were saved because babies went to surgery to have the tumor resected, except that then it became understood that the natural history of some neuroblastoma in infants is to regress spontaneously.

There never had been that high of a death rate, and so the harm was that some babies went to major abdominal surgery for something that would have regressed spontaneously. So there is very little in the way of newborn screening history, but one clear -- this was all in Japan, almost all in Japan, I think, but one very clear evidence of harm from newborn screening without fully understanding the natural history.

With that said, I want to say only two other things. One is, most important is whatever criteria are decided on, they have to be applied

to all applications in the same way, and I think that was a very very very cogent argument for having one case to see the process. I just want to be very sure, speaking as a clinician, that doesn't mean that we need that one case. We can't believe that that one case will teach us about the harms.

Now, I never heard anybody say that it would, okay? You need many cases to understand about harms because we don't want to wait for the one year or the three years or the six months after the ten cases to find the harms. So I have heard a cogent argument about process for one case. I just don't want anybody to translate that into waiting for the natural history of that case. We just want a confirmed diagnosis.

MEMBER TARINI: So I just want to respond quickly to Bob. I agree this is -- that we do this differently in other areas of medicine, but this is public health, not medicine. It is medicine -- it is a public health program that is -- starts in the hospitals, in the clinical setting, but is run, and oversight appears, by the

public health, and we know that because this was the argument we went through with CCHD. So yes, it is medicine, but it is within the public health structure.

And why that makes a difference is this is mandatory, and we are making a decision of going forward. In medicine, we make the decision we think is best. The patient ultimately has the ability to say I don't want to do it, or the doctor has the decision to say I don't think there's enough medicine. Here we are mandating by law that the children undergo it, and we are providing a narrow window or a narrow opportunity for opting out, so I think that that just needs to be remembered. Again, I am not saying either way, but that needs to be considered.

And the second is we can pull back much easier in medicine than we can pull back in public health. There is no precedent from this committee that I know of of removing a disorder, so if we go forward, we have to understand that we also would set a precedent if we think we didn't find a case,

and we would have to come back and pull back. We have no precedent for that right now. And in the process, we will have expended multiple resources across the country in public health in doing so.

And the second is back to this calculation of Alex and the matrix, on some level, this can be done I think on a sort of time assessment. If a disorder does not go to evidence review, it does not mean it can't go again. It does not mean it can't wait a year to go through evidence review and come back to the committee. So if you did a quick back of the envelope and you said, well, we know it should have been caught, we should be having a case by 1 in 50,000, and right now we have 20 -- we have 50,000 screened in one year, we know in a year we'll have another 50, so we should, in a year, we should have two more cases, or we should have at least one. So we know how long it will take based on how many we screen at this rate to get to what we think is a reasonable estimate. So that is one piece of data in terms of time spent or resource expended for time. And then we know how

long it's going to take for the committee to see it and then push it to evidence review.

So in some cases, I think, but I have not done this calculation, you could be talking about a one-year delay. And I think that you have to sort of put this in this bigger context of what is the hedge of time we're deciding on, and I think it is a knowable number.

CHAIR BOCCHINI: Dieter and then Jeff and then Carol, and I think that will probably close the discussion.

MEMBER MATERN: Again, I think when it comes to very rare disorders, it is going to be hard to do this going forward, but I also wanted to mention about the harm and whether any studies were done.

I don't know exactly how we define harm, but I think there are multiple reports and papers out there that kind of indicate what happens with patients that have to go through the false positive scenario. The big ones that I can remember are from the Boston group that looked at the

implementation of the amino acid and ASAL kind of things into screening in January 2003 or so, and then this year, the two papers from the New York group about Krabbe disease, which this committee did not approve, and I think the papers clearly state that that was a good decision.

So I think there is data out there, I think Carol had done a study also about follow-up on what turned out to be false positives and looked at this as well, so I don't know what else we need, because I don't think we need it for every single condition. I think we can kind of extrapolate from the studies that were already done and compare the conditions and their severity and the treatments that would be required, and I think the good news from New York is that nobody got a transplant who didn't need it or shouldn't have had it.

CHAIR BOCCHINI: Jeff?

MEMBER BROSCO: Jeff Brosco. So I have a scientific question, and then maybe follow up with a practical issue.

It sounds like the -- if I listen to

Dieter and I listen to Steve, it sounds like there is a disagreement, maybe a legitimate scientific disagreement, about whether there is something very different about finding a condition using older specimens that are just sitting there compared to the entire process that you described. Is that correct? Is it that there is just a real disagreement scientifically about, you know, using a specimen and getting a positive result?

DR. SHONE: I don't want to sit up here and say I -- let's have a disagreement, Dieter. I think that the difference in the view is the -- what does it show, right? I mean, I don't think -- I think Dieter agrees that testing a retrospective specimen shows the test is valid, right? I mean, that is the whole idea behind this.

My point is simply, and I think Beth articulated it much better, as she is wont to do, and often does, is that if it is not what programs do in real-time, and there is no assurance that the -- that specimen, even though it is thrown in -- let's say it is thrown into the real-time

processing, that does that end up showing that the entire process worked? You are separating out -- I am trying to on the fly think of a process that you do where if you break it up, it might not come up with the same things, and I can try to brainstorm that.

But I think the idea behind what we are trying to show is from start to finish, what we're going to subject four million babies to has demonstrated that it can work.

MEMBER MATERN: Because, again, it is -- there is a test, and the question is does it work to pick up patients? And if you intersperse true positives that are fully diagnosed already, so we know they have the disease, there is no question about it because you wouldn't have asked for that specimen if they didn't have the disease, and you can pick them up, and these are -- the only concern I have, these are old specimens, usually, and how were they stored, and all this kind of stuff, and the risk is that they -- when it is an enzyme activity, you might actually get low activity just

because it is so old and you have to remember that.

If it is a biochemical marker such as GAA, then -- and if it is still high, it is probably true. But you can do stability studies on this and determine this. So there is the analytical part.

And then, again, the follow-up, and through the system, we know that, I mean, since there are, you know, more than 30 conditions on the RUSP and being screened for, we know that the system -- what the system can handle, because it is Carol Greene and the physicians who get the reports, they have to follow up, and they hopefully know what they're doing and doing it right. And if not, then the ACMG has to provide better ACT sheets.

(Laughter.)

MEMBER MATERN: I mean, it is a process that we have to go through to set this all up, and ideally, we should not add anything to the RUSP until all of these parts are put together and have that process lined out from start to finish, what is all needed until it goes on the RUSP? And that might have more stakeholders than we thought.

MEMBER BROSCO: So it sounds like the answer to my question is yes, there is a legitimate disagreement on the science part of this. So I guess I then have a process question, which is -- because I had heard that there was a previous example, and maybe hypothetically, we think of a condition that by all rights meets all of our criteria, but there has not been a positive yet. It goes through the nine-month review, there is still not a positive. We as a committee, because there has not been a positive, have to say no. But can you also have that asterisk like you had before with the other condition that says as soon as a positive comes through prospectively, we can immediately vote on it again at our next meeting? Is that a possible approach?

CHAIR BOCCHINI: Well, I think that is possible, and I think that let's separate the two, because I think that the key issue here is whether we are going to accept the recommendation of the Pilot Study Work Group, which said we need one positive test, and the fact that the people who run

the laboratories believe that that is necessary to evaluate the test in a real-time fashion.

Whether we decide in the future to take the risk of picking something that does not have that in a hope that it gets it, that is a separate question, I think, and I don't think that is one that is up for discussion today. What is up for discussion today is whether we believe that this is an appropriate part of the requirement to bring something forward, and if we in the future decided to bring something forward when this hadn't been met with the idea that we expect it to be met, that is a whole different question, I think. Okay.

MEMBER BAILEY: It's a very interesting discussion, and we could go on for quite a while about this. I guess I would be more comfortable if we, instead of set an artificial criteria of one condition, we said what is it we want to learn? What do we want to know before we make a decision?

So let's take a condition that is 1 in 50,000, and then we say a pilot study gets started,

and on day two, they find one of those conditions, one of those disorders. Have we learned from that -- we're not going to learn anything about what you just said, Beth. We're not going to learn about incidence, we're not going to learn about natural history, we're not going to learn -- there is so much we would not learn from that.

Then, on the other side of it, what if it took 200,000 cases to find one case? What do we learn from that? So I don't -- I am not saying that this is not well intended, or that we're heading in the wrong direction, but I think the fundamental question is what do we want to know from having identified one case? Well how will that help us make a better decision than we would have otherwise? And I am just making some points that I don't think it will answer the questions that some people here have said it would answer.

CHAIR BOCCHINI: Yes, I would agree that this one case does not answer all of those questions. The issue is whether it answers the question in the laboratory about the analytical

validity of the test, and how it would function in real-time.

MEMBER BAILEY: Would one case do it?

CHAIR BOCCHINI: Yes --

MEMBER KELM: Well that is why it is --

CHAIR BOCCHINI: -- and so that's -- I think that --

MEMBER KELM: That is why it is an and, it should evaluate the process and identify, so as you -- I think I agree, if you would mainly have the second part, not the first, if you go through for one, but it's an and.

CHAIR BOCCHINI: Okay. So Carol and then I will let Susan, and then I think we're ready to make a decision.

DR. GREENE: So I think Jeff already implied one of the points -- two points I wanted to make, is that if it is 1 in 50,000 and you don't find one in the first 50,000, you might not find one the next year in the next 50,000. 1 in 50,000 means you could have 4 in the second 200,000. So that is just the sock drawer problem.

So I don't think we can estimate the time. I think the lab is -- all the people in the lab are making a strong plea that they want to have one case, and I think it is very clear that one case does not answer all the questions, and so everything that Dr. Matern has said, you actually have to have that information as well because it is on that that you base your decisions about making a pilot, and all of that is reviewed as well.

So I don't think it is either/or. I think you have to not just say that it would be postponed for one year, because you don't know, it could be three years. There's the funding issues that were brought up. But we also have to use all the information that Dr. Matern was talking about. Clearly, you need what Dr. Matern was talking about. The question before the committee is whether you also need one case.

DR. TANKSLEY: I wanted to comment that the analytical validation can be proven with the retrospective study. There is no doubt in that. What having a screen positive that goes through the

entire process and is -- goes through the diagnostic testing and diagnosis proves the clinical utility of the test.

And so it is two different things that you're proving with the process. You absolutely have to have an analytically valid test, but this is more than just an analytical validation.

CHAIR BOCCHINI: All right. So I want to thank everybody for their participation in this discussion, and Scott for putting his talk together, which I think framed this very well. So here is the statement as it currently reads, and it was modified slightly based on feedback from members of the committee when it was first sent out.

So this is how it reads, the study should evaluate the newborn screening process from collection through diagnosis and identify at least one screen positive newborn with confirmation of presence of the condition under consideration. And so I think we'll just do a roll call vote.

Okay. So -- okay. So I am being told we need a motion to approve, a motion to approve

this as written.

MEMBER SCOTT: I move that we approve.

CHAIR BOCCHINI: Moved by Joan. Second?

MEMBER MATERN: Second.

CHAIR BOCCHINI: Okay. Does any committee member have a conflict of interest regarding this vote and need to recuse him or herself?

(No response.)

CHAIR BOCCHINI: If not, are there any who need or wish to abstain?

(No response.)

CHAIR BOCCHINI: If not, we will go ahead with the vote. We'll do this alphabetically. Don, vote yes in favor or no if not.

MEMBER BAILEY: I have already expressed my concerns and reservations, but in the interest of standardizing the process and moving forward, I vote yes.

CHAIR BOCCHINI: I vote yes. Mei

Baker? Turn on your mic, please. No.

MEMBER BAKER: I am just wondering, the collection, do we need to more specify? Because for us, we understand what collection means, but if out of this committee, you said a formal connection -- I mean, collection, what? Do we need -- if people think not necessary, I am good.

CHAIR BOCCHINI: Well Mei, this is part of a much larger --

MEMBER BAKER: Okay.

CHAIR BOCCHINI: -- thing, and then these are the specific recommendations which are cut short --

MEMBER BAKER: Okay.

CHAIR BOCCHINI: -- but there is more data in the rest of the document --

MEMBER BAKER: Okay.

CHAIR BOCCHINI: -- that supports that.

MEMBER BAKER: I approve.

CHAIR BOCCHINI: Okay. Jeff Brosco?

MEMBER BROSCO: I approve.

CHAIR BOCCHINI: Carla Cuthbert?

MEMBER CUTHBERT: I approve.

CHAIR BOCCHINI: Kelly Kelm?

MEMBER KELM: Approve.

CHAIR BOCCHINI: Fred Lorey?

MEMBER LOREY: Approve.

CHAIR BOCCHINI: Dieter Matern?

MEMBER MATERN: I don't.

CHAIR BOCCHINI: Steve McDonough?

MEMBER MCDONOUGH: No.

CHAIR BOCCHINI: Kamila Mistry?

MEMBER MISTRY: Yes.

CHAIR BOCCHINI: Melissa Parisi?

MEMBER PARISI: Yes.

CHAIR BOCCHINI: Annamarie Saarinen?

MEMBER SAARINEN: I do not approve.

CHAIR BOCCHINI: I am sorry, do you --

MEMBER SAARINEN: No.

CHAIR BOCCHINI: No. Okay. Joan Scott?

MEMBER SCOTT: Yes.

CHAIR BOCCHINI: Beth Tarini?

MEMBER TARINI: Approve.

CHAIR BOCCHINI: And Cathy Wicklund?

MEMBER WICKLUND: I just want to echo what Don said, too. I feel kind of the same way about this, but I approve.

CHAIR BOCCHINI: All right. Thank you. So this is approved by the committee. I want to thank everybody. This was a very important discussion, and I think now, the Pilot Study Work Group proposal has been fully accepted, and now we will work to try and get it in publication form. Thank you.

MEMBER WICKLUND: Can I ask a question, Dr. Bocchini?

CHAIR BOCCHINI: Yes.

MEMBER WICKLUND: I missed the last meeting, but my understanding is there was going to be some wordsmithing of some of the other recommendations from this group, and --

CHAIR BOCCHINI: And in fact, that was -- the proposal had been sent out, and input was -- we have wordsmithed it related to some -- a

suggestion that you had made. But it will go around again so that -- but your suggestion was included.

MS. SARKAR: This is Debi. We also included the revised version in the briefing book, so if you want to take a look, and I can send it out again.

CHAIR BOCCHINI: All right. Okay. So now I know we're behind schedule, but we do have some -- a number of individuals who are here to make public comment, and I would like to bring them forward as they have been listed here so that they have an opportunity to present to the committee and the audience.

So the first is Stephanie Bozarth, with her daughter, Annabelle, to talk about the importance of newborn screening for the degenerative diseases mucopolysaccharidosis II, IV, and VI.

CHAIR BOCCHINI: Welcome.

MS. BOZARTH: Hi. My name is Stephanie Bozarth, and I am Chairman of the Board

of the National MPS Society, and I have with here today Annabelle Bozarth. She is 10 years old with MPS IV-A.

I wanted to talk to you about mucopolysaccharidosis. We also call it MPS for short. It is a devastating degenerative disease that may affect the whole body and almost every organ. It usually takes months to years to diagnose this disease. Prior to diagnosis, irreparable harm is done throughout the body.

So there are 11 different types of MPS. Four of those do have an FDA-approved treatment. That is I, II, IV, and VI. MPS I was reviewed and recommended by this committee, and we are grateful, and we are doing our part to make sure that it is implemented in states across this country.

There is evidence that shows that the long-term clinical effects of MPS treated at birth or in infancy will dramatically slow the disease course and prevent some of the damage from occurring at all. Therefore, early diagnosis and treatment will improve quality of life, reduce

damage to the organs resulting in less disabilities.

In addition, newborn screening for MPS and with improved treatments for II, IV, and VI is critical for the parents and the child to access to genetic counseling, to get family planning, to get proper treatment planning, and to avoid that diagnostic odyssey that parents and children can go through while irreparable harm is happening to their child.

So currently, there are some small newborn screening pilots going on in Washington State for II, IV, and VI. Annabelle I want to talk about for just a second. She is 10 years old, diagnosed with MPS IV-A. She is the oldest of three girls. She was diagnosed at six months old. That was really unusual and also gave my husband and I the chance to family plan for our second two children that are unaffected.

Annabelle, when we first got the diagnosis, it was because I noticed a bump in her back in the lumbar area that was unusual. The

pediatrician completely dismissed it. I got my skeletal survey anyway, we took a look, and immediately, they saw three things growing differently in her bones that led us down the lysosomal storage disease diagnostic process.

It was very good that we went through that process early because at one-and-a-half years old, I went to her crib and found her scratching at her arms, talking about ants. You know, it was very, very concerning. But I knew already what that disease progression was. I knew she was probably experiencing cervical compression, so immediately we went and had the urgent decompression and spinal fusion for my daughter, which otherwise could have led to paralysis and death.

By four years old, she began to walk less because she was in so much pain, and I was giving her Advil and any sort of painkillers all the time. Again, I was lucky. I knew what the disease progression was although she did not look at all like anyone different from anyone else in

that pre-school at that point in time. She still looked like every other child, but we knew it was her hips, we knew it was probably her knees, and we did find that we needed surgical intervention to be able to get her back up on her feet and walking again with reconstructed hips.

Then, by the age of five, her stamina, her shortness of breath, her endurance was lagging. She was not playing like the rest of the kids. She was resting too much. And we knew the disease progression was taking its course. Fortunately, enzyme replacement therapy started -- was in a clinical trial for MPS IV-A, and at five years old, we got her into that clinical trial. Within months, we saw her endurance improve, her shortness of breath improve, and I was able to put away the Advil that I was giving her two times a day. ERT for MPS IV was approved in 2014.

In review, we were very very lucky with our diagnostic process, but this is not normal. Most children with MPS, any of the MPSes, are not diagnosed until the ages between three and five,

and by that point, irreparable damage has already happened. We know that if Annabelle had gotten that ERT, if it had been available at birth, there is a good possibility that her outcome would be different. She might be a little bit taller. She might be able to reach the sinks in the public bathroom. Life could be really different for her.

That is why we feel that newborn screening for II, IV, and VI that do have FDA-approved treatments must be part of this coming up for nomination soon, and we hope to talk to you more about that in the future.

CHAIR BOCCHINI: Thank you very much for coming.

(Applause.)

CHAIR BOCCHINI: Annabelle, thank you for bringing your mom.

(Laughter.)

CHAIR BOCCHINI: Okay.

(Laughter.)

CHAIR BOCCHINI: Next, Shannon Zerzan talking about newborn screening for spinal

muscular atrophy. Welcome.

MS. ZERZAN: Good morning. Dr. Bocchini and members of the committee, thank you for the opportunity to testify today.

My name is Shannon Zerzan. I am the mother of a son with spinal muscular atrophy, the leading genetic cause of death for infants. Since our son's diagnosis, we have worked closely with Cure SMA to raise awareness and funds to support their mission of a world without SMA.

Cure SMA supports and directs comprehensive research that drives breakthroughs in treatment and care and provides families the support they need. On behalf of Cure SMA, my family, and thousands of other families affected by SMA, I am here to comment regarding the committee's consideration of adding SMA to the Recommended Uniform Screening Panel.

Over the last decade, there have been significant advances in the development of a treatment for SMA. In fact, earlier this month, we were pleased to hear that a partnership between

two biotechnology companies has resulted in closing the Phase III clinical trials of a treatment for infantile onset SMA based on an interim analysis showing that the primary endpoint was achieved.

We are now at an exciting precipice, with a potential for seeing an approved treatment for SMA with the likely filing of a new drug application to the FDA later this year. Both human natural history data and animal model data suggests that early drug intervention allows for the greatest efficacy in SMA treatment in the most common and severe form of SMA, Type 1.

Diagnostic delay is very common in SMA. It can take weeks, months, and in milder forms of the disease, even years to accurately diagnose. Early identification of the disease can prevent this diagnostic odyssey with subsequent physical decline.

Preliminary data and mouse models also indicate that pre-symptomatic drug intervention is more effective than post-symptomatic, with the

results being remarkably consistent. In the most severe mouse model of SMA, the efficacy of drug treatment has been shown to diminish substantially after the first week of life. There is now a pre-symptomatic clinical trial in progress in human infants to validate these findings.

Most parents of children born with SMA leave the hospital with a healthy baby, and everything seems fine until it is not. One study has shown that infants with SMA Type 1 demonstrate normal motor neuron innervation during the pre-symptomatic phase of the disease but suffer rapid and severe loss of motor units during the first three months of life. This can result in the loss of more than 90 percent of motor units by six months of age.

Pre-symptomatic intervention and drug treatment is not possible without pre-symptomatic diagnosis. It is of the utmost importance that SMA be added to the Recommended Uniform Screening Panel to ensure patients and families are made aware of the disease through newborn screening, told of the

need for treatment, and obtain treatment as early as possible. The very real promise of a successful treatment, coupled with the significant advances in supportive care, will change the course of the disease and quality of life for these children.

In conclusion, the SMA community strongly urges the committee to consider the forthcoming SMA nomination in light of the speed with which we are moving toward an effective treatment, the availability of affordable and validated screening tools, and the demonstrated benefits of early intervention.

I thank the committee for the opportunity to address you today and appreciate your consideration of our views.

CHAIR BOCCHINI: Thank you, and thank you for your presentation.

(Applause.)

CHAIR BOCCHINI: We certainly look forward to the emerging data and receipt of a nomination for looking at SMA.

Next is Kristin Stephenson to discuss

newborn screening for neuromuscular diseases including SMA and Duchenne muscular dystrophy.

MS. STEPHENSON: Hi. Thank you for the opportunity to address the committee. My name is Kristin Stephenson, and I serve as Vice President of Policy and Advocacy for the Muscular Dystrophy Association, and I am here today representing tens of thousands of families and individuals who are living with muscular dystrophy, spinal muscular atrophy, and other neuromuscular disorders.

MDA is a national nonprofit organization dedicated to saving and improving the lives of people living with neuromuscular disease. To this end, MDA funds research, supports more than 150 care centers nationwide, and champions policies and programs important to those we serve, such as the public health program that is newborn screening.

We are pleased that Pompe has been added to the recommended panel and aim to work together with the community to see other neuromuscular

diseases included as well, such as MSA and Duchenne muscular dystrophy. With considerable advances in the therapeutic pipeline and with current studies in process to develop the requisite data to support the application for nomination to the RUSP, we believe both SMA and DMD will prove strong candidates for addition to the panel, and we urge the committee to support those nominations as they are submitted.

Multiple therapeutics to treat both disorders are moving forward, and a well-established nationwide network of care centers exists to provide follow-up care to infants as they are identified through the screening process. We are pleased to be part of a robust and collaborative effort to move newborn screening forward for both disorders. The community is preparing for newborn screening in these diseases.

We have recently entered an exciting phase as researchers have identified the genetic causes of many neuromuscular diseases, and precision medicines are in development to target

the underlying cause of disease. SMA, as you just heard, is the leading genetic cause of death for infants, and the pace of therapy development in SMA is unprecedented. The causative gene was only discovered a decade ago, and we are now seeing the first human trials testing therapies that target the underlying cause of disease. There are currently seven therapies in clinical trials for SMA, with over a dozen other approaches nearing the clinic.

Innovative strategies such as gene therapy and antisense oligonucleotide therapy are also being tested and are showing encouraging data. Recently, a large SMA Phase 3 trial was halted due to the trial meeting its primary endpoint in an interim analysis. We hope in the coming months to witness the first filing for a new drug application for SMA.

Similarly, there are now 30 drugs in clinical development for Duchenne, and the FDA is currently reviewing potential treatments. Notably, the use of corticosteroids are currently

in place for Duchenne, and their use is being studied in pre-symptomatic infants.

Time is of the essence in implementing newborn screening for SMA, DMD, and other neuromuscular diseases where early treatment is best and perhaps the only impactful approach to alter the natural progression of the disorder. The significant drug development efforts are encouraging, and we hope many of the other disorders covered under MDA's umbrella will follow in a similar path. In addition to SMA and Duchenne, there are infantile forms of other types of muscular dystrophy and other neuromuscular disorders that could benefit from early intervention, and we look forward to sharing the information with you about these and other disorders in the future.

Thank you for your time today and for helping save and improve the lives of newborn and children who have or are at risk for heritable disorders.

(Applause.)

CHAIR BOCCHINI: Thank you very much. Thank you, and thank you for the work of the MDA.

Next is we have Kim Tuminello and Heidi Wallace from Association for Creatine Deficiencies, will discuss newborn screening for GAMT deficiency. Welcome.

MS. WALLACE: Good morning. It is good to be back here. Actually, I wish I wasn't coming back. I wish things had gone better last time, but while there is much discussion regarding evidence and the precise wording of guidelines, I am here to remind you about why we're all here today, and it's our children.

I have a group of children that represent about six months of births in the U.S. This is Ella from England, Grace from Canada, Tanner from Wisconsin, Carly from Louisiana, Celia from Chicago, Trinity from Delaware, Raphael from Michigan, Ryan from New York, Paige and Ty from California, Theresa from Ohio, Levi from Utah, Caden from Ontario, Canada, John from North Carolina, Max from California, Benny from Chicago,

and finally, my two children, Samantha and Louie from Utah.

As you can see, that is a lot of children in six months' time that are born in the U.S. After years of missing all of her milestones, Samantha was diagnosed as having autism at age three. Finally, at five and a half, she was diagnosed with GAMT and began treatment. She recently turned 13 and started middle school, where she attends the intellectually disabled classroom.

We battle with recurrent seizures that do not respond to anti-seizure medications. She will require lifelong care.

My son Louie, with the same genetic mutation, will soon turn five, and he was diagnosed at birth because we knew to check immediately. He began taking creatine, l-ornithine, and sodium benzoate immediately. His dosages have been adjusted based on established treatment guidelines as he has grown. He spoke and was potty trained all before three, the age at which his sister had done neither of those and was diagnosed with

autism. He is beginning his last year of pre-school and has already passed off his kindergarten readiness test. He scores cognitively in the typical range.

There is an abundance of knowledge gained from Sam and Louie. One, GAMT not diagnosed at a very young age is devastating. Two, GAMT diagnosed at birth leads to a full life. Treatment works. Three, screening for GAMT works. Louie's newborn blood spot was used, de-identified, in testing at ARUP to establish the efficacy of screening for elevated levels of guanidinoacetate. In the testing of thousands of dry blood spots, Louie's came up as the one true positive.

Further, evidence has been established that the level of guanidinoacetate in a newborn blood spot does not change over time, making retrospective studied very informative. So prospectively, as in Austria, and retrospectively, as with Louie, a GAMT dried blood spot does come up as positive when tested using mass spectrometry.

Thank you for hearing from me today.

(Applause.)

MS. TUMINELLO: Good morning. Thank you for allowing us the opportunity to speak to you again this morning. For those of you that weren't here, for the new to the committee, my name is Kim Tuminello. I am the President of the Association for Creatine Deficiencies.

A few months ago, four of us from the ACD were here speaking about the urgency of newborn screening of GAMT. As we discussed, this severe neurological disorder is treatable, affordable, safe, and life-changing, but only if caught early in life.

The disappointing loss of just one vote here in May was something that I understood because of the enormous responsibility I know that you all hold making sure that all the criteria is met. Many of you graciously approached us and told us not to give up and urged us to come back.

There were two remaining parts of the criteria that were required. The first one was the

treatment guidelines that we all knew would be easily met, since those affected around the world have been using a standard treatment successfully for years. However, the second one of finding a newborn prospectively seemed too far away. I thought to myself, and many of you also asked the question, how many children will be missed in the time that it would take to find one more positive newborn on the pilot in Utah? I even looked at poor Heidi over there, wondering if she would be willing to reconsider having more children.

However, shortly after the meeting in May, we were given the pilot study of Dr. Bodamer's, and there it was: the one positive screen of GAMT on a newborn baby in Austria. The baby proved that the technology could indeed pick up the elevated guanidinoacetate at birth prospectively.

There is no doubt that there is a family out there who is going through the same agonizing odyssey with their child that my family did. I will tell you that personally, after months of doctor's appointments, tests, waiting for results,

therapy, lots of tears, and spending countless hours on the computer, I realized that it was not going to -- I was not going to figure out what my son had on my own, and I gave up.

That night, I dropped to my knees and I prayed. I vividly remember begging God for my son's life. I prayed for something rare, for a diagnosis that no one had ever heard of, for it to be treatable, and if it was, I promised that I would spend the rest of my life helping others with whatever it was.

Not even a week later, my husband and I received a call from Rady Children's Hospital saying that they knew what it was, it was extremely rare, but it was treatable. My son Ty was the first one in the U.S. diagnosed with GAMT. It was at that moment I knew what my mission was. Well, here we are today. I made a promise, and I'm sticking to it.

Please don't let this committee's true mission of getting kids diagnosed go unaccomplished. Families are depending on you and

I to get this done. Please get this voted on as soon as possible. There is no time to waste with these children's lives at stake. Thank you.

(Applause.)

CHAIR BOCCHINI: Thank you both very much. Appreciate your comments.

And now, Dr. Nicola Longo and Dr. Marzia Pasquali to talk about newborn screening for GAMT deficiency.

DR. LONGO: Thank you, Dr. Bocchini, for giving us the opportunity to speak, and for the continued consideration of the inclusion of GAMT deficiency in the Newborn Screening Panel. My name is Nicola Longo from the University of Utah, and --

DR. PASQUALI: Marzia Pasquali from the University of Utah.

DR. LONGO: So we have proposed this condition because obviously we have seen quite a few patients with this condition. We just wanted to provide an update on the initial application.

So first of all, we have included the

Association for Brain Creatine Deficiency Syndrome in denominator because they have been a strong proponent of the inclusion of this condition in the Newborn Screening Panel. There are new data on the frequency of false positive result, which is something that always make us upset because we have to calm that family. And now, we have completed about one year of screening, and we found 1 false positive in 60,000.

They had similar results in British Columbia, where they did a retrospective study where they found 1 positive result in 45,000. So the false positive rate that we knew was less than 1 in 10,000 we now know is between 1 in 45,000 to 1 in 60,000, which is a very low false positive rate. I do not know of any other condition which has such a low false positive rate.

The screening is continuing now in British Columbia and Utah. Still the number of births is relatively low. It is less than 100,000 births every year in the two places combined.

The second thing, there was a mention

of the finding of Dr. Bodamer, so we contacted Dr. Bodamer, and the positive screenee was found in screening 30,000 newborns. So he found 1 out of 30,000. Obviously, at the time, the perfect way of confirming the diagnosis was not known. He screened the urine. We now know very well that we need to screen blood, and obviously, that patient would not have been missed by the newborn screening done today.

And the second thing is that some of the patients -- you know, one of the requirements that was discussed to satisfy all of the requirements was to demonstrate that the system works. And some patients actually had been tested at birth with other means and treated at birth, closing the loop. The treatment of these patients at birth, even though it was not diagnosed prospectively by newborn screening, demonstrated that the system indeed can affect the lives of these patients, leading to first diagnostic demonstration, and finally, to the -- achieving the treatment.

The last question is -- was about the

treatment. I mean, in the papers that have been published, some of them -- one of them was a historical paper where all of the treatment that patients did was listed based on the time where they were diagnosed, and many of them had outdated treatment. Our latest manuscript that was actually part of the evaluation, we also raise the same question, but you know, that was in the introduction. But then, when we were in the discussion, there was an agreed-upon treatment that every specialist in the United States, Canada, and Europe used, which is the combined use of creatine, ornithine or sodium benzoate when tolerated, and imposing a restricted diet.

Obviously, treatment needs to be tailored to every patient because, you know, especially when you start a diet in patients that are older than three years of age, it is not very easy, and obviously, like every medication, it needs to be adjusted to every patient. We hope that this additional information keeps the screening for GAMT on the radar for this committee,

and we hope that the condition gets approved very soon. Thank you for your attention. Thank you.

(Applause.)

CHAIR BOCCHINI: Well thank you for your comments and presentation. And as you know, we would continue to work with you for an updated nomination packet that includes the additional information that you have discussed so that we can look at that and bring it back to the Nomination Prioritization Work Group, so thank you, appreciate it.

Next, Jackie Seisman, newborn screening education for midwives. Ms. Seisman?

MS. SEISMAN: Good morning. I first want to start by thanking members of the Advisory Committee for giving me the opportunity to provide public comments today.

My name is Jackie Seisman, and I am the Program Manager for Expecting Health and Genetic Alliance. This summer, our team worked on developing educational guides on newborn screening and home births. One guide was targeted toward

midwives performing home births. Another guide was designed for expecting families considering a home birth.

To help inform the creation of these guides, and also to gather insights on these communities, we interviewed midwives and midwifery practices in the D.C. metro area as well as groups outside of D.C., including a midwifery practice in Texas. Through these interviews, we learned of the immense needs and barriers that exist for both midwives and parents when it comes to newborn screening.

For midwives performing home births, their ability to conduct newborn screening, including the heel prick, pulse ox, and hearing screening, is severely limited by costs and both the ability to obtain proper and updated equipment. For midwifery practices sharing pulse ox or hearing screening equipment, for instance, scheduling conflicts among midwives and conducting home visits for families in rural or remote areas makes conducting newborn screening in a timely fashion

difficult, if not impossible.

Additionally, while most midwifery groups we spoke to conduct the heel prick 24 to 72 hours after birth, this is only if they have access or can afford the newborn screening cards. If they do not perform the heel prick, midwives will refer family members to a provider or a hospital. Midwives noted that this is -- it is actually quite common that during their two-week home visit, that the newborn screening for the infant never happened.

For families choosing home births, making sure newborn screening happens within the first 72 hours is complex, from having to schedule multiple appointments ahead of time to ensuring that their health provider or midwife has the appropriate equipment. This is only intensified from the lack of information or resources new parents receive about newborn screening, including its importance and urgency.

While this is just a small snapshot of some of the barriers that exist, the percentage of

U.S. women choosing to give birth at home or in a birthing center has steadily been growing since 2004. It is important that we have a system in place that supports families that choose to give birth at home and that provides midwives with the resources and ongoing training needed where they feel confident in both conducting newborn screening and educating families. This means partnering with midwives, identifying trusted sources of information, and using both traditional and non-traditional communication channels to reach both midwives and families choosing and considering home births. Thank you for your time.

(Applause.)

CHAIR BOCCHINI: Thank you very much. This is very important information for the committee and for the whole -- for the health of women and their babies, so we need you, if you would, to talk further later on. Thank you.

With that, I know we're running late, so we're going to take a 10-minute break really quick. Come back on time. We are going to start

in 10 minutes. Thank you.

(Whereupon, the above-entitled matter went off the record at 11:07 a.m. and resumed at 11:23 a.m.)

CHAIR BOCCHINI: All right, let's go ahead. We're going to start this session of the meeting.

We're ready to start. At the last meeting, there was some discussion about new technologies and disruptive technologies and how things might affect newborn screening. We have the pleasure, today, of having Dr. Michele Caggana here to give us an introduction to sequencing and potential impact on newborn screening.

Dr. Caggana is board certified in clinical molecular genetics by the American Board of Medical Genetics and a fellow of the American College of Medical Genetics and Genomics. She's deputy director of the Division of Genetics, chief of the laboratory of Human Genetics, and director of the Newborn Screening Program.

She's involved in many national newborn

screening efforts, including the national pilot for Pompe disease implementation, and works with the Centers for Disease Control and Prevention and the Association of Public Health Laboratories. Her laboratory has developed several newborn screening tests and uses DNA technology to study frequencies of specific gene mutations in dry blood spots in the context of newborn screening.

So, Dr. Caggana, welcome. Look forward to your presentation.

DR. CAGGANA: Thank you, Dr. Bocchini, and thanks for the invitation. What I'm going to talk to you today -- my task for you is to set the stage for what's currently going on in newborn screening programs related to molecular technology and to discuss and talk about some of the things that we're working on in concert with other state programs with the CDC and APHO. Some of you have seen some of these slides before, so you can view it as sort of a refresher course.

So just to get everybody on the same page and reiterate, the purpose of newborn

screening is to assess risk for disease. The tests that we develop have to be universally available, and they also have to be timely. We've heard a lot about that lately. And so the goal of newborn screening is to find the one baby who's at the highest risk for one of the conditions that we're screening for.

Along with that, having a program where we have to assess the health status of, in my state, 250,000 babies, across the country, 4 million babies a year, we also have technology that's on the increase. So this slide I got from Suzanne Cordovado from CDC and it talks about the declining costs of genome sequencing, and I did a couple of envelope calculations here to talk about my lab. This new instrument produces 16 human genomes in three days at 30X coverage if you do sequencing.

In order to handle my daily load, if we were going to go to this, which I'm not saying we are, I would have to buy 63 instruments, at $10 million apiece. That's a lot of money. Even at a nice cost of about $1,000 a genome, it would cost

my program somewhere around $250 million to do this for every infant that's born in New York. And those costs don't include the overhead, infrastructure, service contracts, and all the associated costs that come along with introducing these types of technologies, and the instrument cost, like I said, was about $10 million per instrument.

So the bottom line, the thing that we really are interested in learning about is does the molecular testing that's happening right now in newborn screening programs, if we were to expand it, does it add value? My sort of association with this is, does it clear things up for us, or does it really muddy the water? In the context of newborn screening, we really want to make things clear. We don't want to make things worse for families.

So we looked for some goals we're interested in and we have some goals of why we would want to implement molecular testing in these programs, and one is to increase the sensitivity

or effective specificity of a biochemical test. Things that come along with that are we identify carriers and we can look at these as problems, or we can look at them as teaching moments. It does work both ways.

How we make predictions regarding phenotype -- sometimes we can do that, and sometimes we cannot. Over time, we hope that these predictions will increase, and that we can better assess the health status of an infant who's asymptomatic by doing some molecular testing and giving some genotype data.

The clinicians' perception of molecular testing is that if you have a delta-F508 homozygote for CF, the baby has CF, and therefore, I don't necessarily have to do a sweat test. A lot of times clinicians use the molecular data as the diagnosis, and sometimes that's good, and other times it's not. The impact, I'll talk to -- I'll give you a couple examples from our lab on the impact of molecular testing as another tier of newborn screening and the impact that that has on

timeliness, which is another issue that's on our minds quite frequently.

So what I wanted to do was talk a little bit about where we are currently and where we potentially can go, and then, as I said, give you some examples. So most of the time, in newborn screening programs, we're using second-tier tests after a biochemical test. And again, one of the good examples we use for this is to increase the specificity of cystic fibrosis testing.

We also help sometimes to clear up an ambiguous result. We can do a just-in-time assay to give a clinician more information at the time of the referral. So most often, it's used as a second tier. The one test that's being done almost universally, not quite, but pretty soon universally, is testing for SCID, severe combined immunodeficiency. In this case, we're not looking at genomic DNA mutations. We're actually looking at a TREC value that we assess by extracting DNA from every infant that comes in the door.

We also have a pilot study looking at

spinal muscular atrophy, and that's only done on a consented pilot basis. In 2015, the CDC's proficiency testing program from the quality assurance program -- they had 23 different countries participating in their PT for molecular, so it is fairly widely used across the country and the world.

So what things do we need to consider from a newborn screening perspective? Number one is always cost. I just threw out some dollar amounts, so that you can get a sense of -- great technology, a lot of information, but how much is it going to end up costing us? What's the value added, the impact on turnaround time, and how much staff time, and what are the qualifications of staff? State programs often have civil service titles that they need to fit into these types of high-tech jobs.

The bioinformatics needs -- where do we store data? How long do we store data? How do we analyze the data? How much time is it going to take us to analyze the data? The requirements for

instrumentation, practical issues, such as rooms, workflow arrangements and that sort of thing, and a question of are we a screening program, or are we a diagnostic laboratory? And the two get very blurry when you start talking about genotype data.

Back in the old days, to sequence a gene, it was art. You had to pour a gel, and you were lucky if you got a gel that looked like this, and with a really good run, you could read several hundred bases by hand and either write down the sequence or type the letters into a computer. It was a very good -- you know, on a good day, you could get 800 bases. We used to load 96 wells on a gel, and that meant you could do about 24 fragments of DNA at a time. It took pretty much all day, and beyond, to get that done.

With the advent of the Human Genome Project, we went to a fluorescence-based sequencing and now, we could expand the number of bases we could collect. We could expand the number of instruments we could collect. It was still a little bit of art, not as much, much more automated.

And we could set up these genome centers, where we had a lot of these instruments side by side. This is a picture from the Broad Institute. This was still the Sanger sequencing method.

Now, we've moved beyond that, and we have these boxes where you sort of put stuff in and it will download to a computer, and then there's a lot of analysis at the other end, and you have much more throughput. You have many, many more bases at a time using these types of technologies. So from the late 70s, mid-80s until now, it's been really an advancement in the field.

So we have this sort of view of newborn screening that we just plod along and we do what we're supposed to do every day. The samples come in. We have to test them. We have to get the babies out to care. We have to get a diagnosis back. And we have to have instrumentation that's relatively cheap, that we can get multiple copies of, and that's reliable. Out there on the market, there's the cars like this, which is my dream, but, you know, a tire for this car costs a

whole lot more than a tire for that car. So we need to consider that in the context of having enough instruments to able to do the screening that we have to accomplish every day in a timely fashion. So reliability is key.

This shows you basically sort of the status of where we are from the newborn screening perspective with molecular testing. Right now, as I said, we do genotyping of a single gene, some mutations in that gene, and that gives us an assessment of the health status of the infant.

Our laboratory sequences some single genes. We use the Sanger methodology now. There are some other -- Wisconsin's doing some work with CF and next gen. California does CF by Sanger. Next, you may think about looking into sequencing panels of genes to help us find out some more information about the infant. There are companies out there right now that clinically offer sequencing of the panel of newborn screening genes, not a panel of mutations in a single gene, but the broad base, and then, of course, the end game would

be just to sequence everyone's genome or exome. We're not there yet, but that is offered clinically.

This just shows you that first green level here. We have the CF gene. We look at some mutations that cause CF after we get a biochemical test. The biochemical test, the IRT, is not so good, so in this case, having some mutation data actually helps us out. Galactosemia, the biochemical test is quite good. Some labs do a panel of mutations to give more information to the clinician and improve sort of a just-in-time because the enzyme could be compromised by weather, and there's some other issues with galactosemia that maybe the molecular diagnosis helps out.

In our laboratory we have screened since 2006 for Krabbe disease, and when we developed the biochemical test, we decided that we also wanted to look at a DNA-based tests of the GALC gene. So we were able to implement this test using a Sanger sequence for GALC without really losing any timeliness. It didn't really cost us much in

time.

We do the biochemistry test first, and if that's positive, we do the biochemistry test again in duplicate. So in Joe Orsini's laboratory, he does the enzyme assay. If he gets a positive on that first day, he comes back, lets us know, and we start the DNA. If his results all show low GALC activity, we move and we finish up the sequencing, so we've already sort of started the process. And what we've found out is by doing that, we've actually reduced the number of referrals, and this number has held consistent for quite a long time. 41.3 percent of referrals get reduced. By doing DNA, we can exclude babies with low enzyme activity, yet have no mutations. The end result there is they get the information in time.

The clinician can talk to the family about the mutations, in some cases, or they don't even know they had a positive screen in others because we found out that they don't have any mutations. So we've increased specificity, and

we've decreased familial anxiety. That's one of the things that we're very cognizant of and work hard to decrease anxiety in families.

So there's a challenge in doing this. We've talked a little bit about -- this morning, the fact that whether a baby is asymptomatic when they have a positive screen, or when we look at screens from infants who we know are symptomatic, that gives us a little bit of information. Most of the data out there is known from people who were actually diagnosed by symptoms. But a newborn screening, we're looking at children who appear healthy and trying to say they are at high risk for one of these conditions.

And so right now, one of the major challenges here is determining the pathogenicity of a variant that we detect. We run about a 25-30 percent rate of novel mutations in Krabbe, and even some of the other genes that we look at. So if it's a known pathogenic, that's pretty easy, and if we know it's benign, that's pretty easy. But we run into a lot of trouble with these three here, that

are in pink or reddish. What do we call these, and what do we tell a family whose babies screen positive, and now we find a variant that we don't really know -- we can't really tell them what it means and what the outcome may be for that child?

Luckily, there's a lot of efforts out there where knowledge is accruing to try and figure out what those variants mean, but right now, we're in this limbo of trying to make these calls based on what's out there and what's been deposited in various databases and what various prediction software can tell us. And so it gets a little nerve-wracking in the middle here.

I've used CF as a model here and I'm going to show you how, in this instance, we're working on a process that's going to definitely reduce parental anxiety, but it's also going to cost us some time. Most referrals for CF with IRT and one mutation or no mutations do not end up having cystic fibrosis. So we base it on this first-tier test here, and then generally, laboratories who do DNA do a panel of mutations.

It's only a very small subset of all of the known mutations that cause cystic fibrosis, and so we're picking what we think are the most common for our population. We're bound by what's available commercially in a lot of cases. But we also that all CFTR mutations don't cause classic CF. There's a major effort now with the CFTR 2 database trying to classify the variants, and it's really helping us out a lot, and so we do have information that's emerging and building to help us with interpretations.

So if you look at the New York State algorithm, we did a look back of three years, and we do the IRT assay. We have babies who are normal, in the bottom 95 percent of IRT, who screen negative, and we forget about them. They're good. We go to the next step and it gets a little bit more complicated. At the time we were doing the Hologic panel, from 2010 to 2013, and we could have several outcomes after the DNA test. We could have two mutations, one mutation, and we also had a category in New York of very high IRT. We had, I think, 22

cases over that time frame of infants who had very high IRT, but no mutations detected. The majority of those babies were non-Caucasian babies, but they ended up having positive sweat tests and had high IRT.

We referred many more babies than the 22 that we picked up, but we were able to pick up that group. If you have two mutations, it's pretty straightforward. They would get referred. If they had -- and most of the babies who are confirmed have two mutations, so in that time frame, there were about 30 to 40 referrals, and 19 to 37 cases per year.

But if they had one mutation, because there's so many other mutations that cause CF and we're always worried they have the one that's not in our panel, we also refer those kids. In that population, most of them are healthy carriers. And we don't pick up all carriers, either. Most of them are carriers, and we got a pickup of 9 to 26 cases. You can see that the number of referrals has increased significantly in the one category,

and it gets much worse.

The very high IRTs, we had 250 referrals for one to four cases in that group. So all in all, we ended up having 900 referrals for 29 to 65 cases over that timeframe. So we looked at other means to be able to do the testing.

What we wanted to do was take a look at what yield we had, what sensitivity we had in our Hologic panel. Could we do a much larger targeted panel and pick up babies? And indeed we do, the sensitivity increases. Then if we looked at the entire gene, what would impact would that have on sensitivity? On this side here is the number of infants that were referred. I think there's a typo on that other slide -- many more referrals in that category, in the high IRT category.

So in this case here, we were able to pick up 256 babies who had two mutations, but when we increased the panel and ran those same -- that group again, we picked up 300 total. I'm sorry. When we went here, we were able to remove some babies that were one mut to the two mut, and move

some babies that were in the very high IRT up here, so this number built up.

Then again, when we went to the clinical sequencing assay, the same thing. By the sequencing assay, we ended up having no babies left in the high IRT. They ended up having either one or two mutations. And so you do increase sensitivity in this group if you go ahead and sequence the entire gene.

So what we propose to do in New York is a different type of algorithm. We start off, obviously, with IRT, until we get a better first-tier biochemical test, and then we have the same idea, but we're going to try -- we're developing a two-seat panel, which is a New York-centric, if you will, group of mutations that we found in all of our diagnosed cases, a la California and how they started out their screening. We found that we couldn't live with reducing the IRT value in our cases, so we're keeping it at the 5 percent.

So the two-seat panel is going to first

interrogate all of the New York-specific mutations, and then the idea is we would move on from there. The very high IRT values, anybody who went to two muts would be referred. We'd no longer have that referral category. If they had one mut, it would go to two mut, and we would refer, and this is after we would take those babies with one mut on the 139 or 150 gene mutation panel, and what we would do then is open up bioinformatics and look at the entire gene. We would sequence the entire gene on the first tier, but only look at a certain subset of mutations.

And so we did that -- plan to do that in our validation study, which is ongoing in our lab right now, and the two mut babies obviously wouldn't change. The take-home message is that by doing that, we would reduce our referrals from 900 roughly per year, all the way down to 100 per year by implementing this New York panel plus this bioinformatics second look in kids who had one mutation, or no mutations but high IRT on that first cut.

So this is sort of a summary slide, looking at our birth rate. Our first tier would be, first, those babies who ended up with a high IRT value. We do somewhere between -- we do about 15,000 tests a year. We do a lot of repeat tests before we release the genotype data. The second tier would be to look at these babies using the New York sort of panel, and anybody with one or two muts would give us about 900 infants.

And then when we opened up the whole gene and looked from that same test run, now we're down to the 100 babies being referred. We think that would really improve our test, but it's not really without a delay. So we would reduce the number of referrals by 89 percent, but if you look here, these are the day that this happened. Day 1 is accessioning. Day 1 is IRT test. Abnormal results on Day 2, repeat IRT. Then we extract DNA. We do the mutation screen. Any positives are re-extracted and the screen is set up again. Then we enter results, and the results are actually sent out on Day 5.

If we add this extra sort of test here using the next gen technology, minimally, our results are going to go out on Day 7. That's if everything -- that's after receipt, that's not after birth. So the difference here is that we're going to increase the amount of time, but cystic fibrosis is not necessarily a time critical condition in the sense that urgent diagnosis is required, and we'd be able to get those results in a time that's usable for the families, and we would impact far fewer families. This also doesn't account for any batching we might do. This assumes we do this every single day.

And the other example I wanted to show you is a project that's ongoing in our lab. We're going into year two of this grant looking at SCID. This idea is to move a post-analytic test into the analytic phase of screening. SCID is a good example because there's many different genes that could cause various forms of SCID.

Our immunologists felt they could provide better care and have more universal type

testing of infants who had a positive TREC result if they had the mutation data as well, when they saw the family. Right now, this is done post-analytically. We refer based on TREC values, and then the clinician may order gene testing, and he may do it or she may do it either a panel or a gene -- one-off gene testing, which becomes difficult.

If we could provide the timely mutation analysis, they would have this information early on when they saw the family. We feel that when Public Health provides this analysis, we can ensure healthcare equality. We don't have to worry about insurance coverage for the child, other siblings, etc.

So we measure TRECs, and anything less than 125 TRECs in New York constitutes a referral. And as I said, a panel of tests is ordered and often, part and parcel to that is a multi-gene panel that is ordered when the flow studies -- or after the flow and mitogen studies come back. It can be a slow and iterative process.

So for our grant, we're validating two platforms, looking at a 39 gene panel, to see whether to not we could get information on the various genes that are known to cause SCID upfront. We want to evaluate which platform works best in a newborn screening setting and/or what's required, and what's the turnaround time for this testing, and do we actually get a shortened time to diagnosis? Does it result in fewer visits to a specialist? Do we have better targeted treatments?

And we're going to initiate long-term follow up for these children. So right now, we're in the process of validating both platforms, and we're working on Sanger sequencing a set of known SCID patients, where we have the genotype data from the provider to make sure that everything is working according to, you know, how it should and what's already known.

This is the panel of genes that will be looked at -- or is being looked at. We're not doing this prospectively yet. Right now we're doing the

retrospective validation. So that's kind of where we are with sequencing in our laboratory. The next step along the way is to do sort of this model pathway, this biochemical pathway. This way, we can look at some modifier genes for these pathways. Maybe we can make some better predictions about genotype and phenotype, if we knew more about the entire pathway. Maybe we could parse out an infantile from a juvenile from a later onset case, which is a big problem for a lot of the lysosomal storage diseases, as people who are screening right now for Pompe and Krabbe and some of these other conditions are very well aware of.

The next step along the continuum here is to just put together a panel of all newborn screening genes and do a two-seat type of approach, where you would look at this panel as a second tier, after a biochemical abnormality is detected, and then only look at some of the genes that are relevant to that biochemical defect, sort of turn everything else off and look at the newborn screening condition that flags on the biochemical

test. This way, it's easily modifiable. You can add new genes in, and you get some economy of scale in programs, and the data's still manageable at this point. You're still going to have time and energy, hopefully, to be able to analyze the data and report out in a just-in-time way.

We're looking into doing this in New York and establishing what we're calling a newborn screening corps. It's down the road a little bit yet because we have some other projects that we're doing, but that's certainly on our radar.

And then as I opened with, the whole exome -- or the whole genome analysis, everyone in this group's probably aware of all the issues that would come from this type of analysis if we planned on doing this type of screening for all babies, or even a subset of babies, it still would be not very manageable in the world of a newborn screening program.

So points that we still need to think about, when you think about sequencing in the context of screening, is are we going to make it

better for families or easier for families? Would we alleviate or increase the burden to them? What about variants of unknown significance, and misclassified variants where you tell them the state of the knowledge today, but maybe down the road in a year or two, that variant changes classification? How do you go back to those families?

Sometimes we can't find them two weeks after -- you know, when we're looking for them when they're two weeks old. To go back to them several years later and kind of give them the new information might be a big challenge for programs. Our screening programs will now be just basically big diagnostic programs. The molecular diagnosis, as we know, may not result in a phenotype immediately, so now you've created this whole population of patients who are waiting for something to happen.

Providers need education to be able to relay the information, and there really has to be a huge influx in genetic counselors out there to

handle the load that this would create.

How we think we could probably do this right. Okay, so I like the glass half full approach. In concert with CDC and APHL, they support the molecular subcommittee, which is a subcommittee of the Newborn Screening, Genetics, and Public Health Committee. We have some expertise in newborn screening. There's people that are actually doing the sequencing in several state laboratories. We collaborate all the time.

We just want to be smart about how we do this, so we want to do a step-by-step approach, kind of more like the Toyotas, and see if we could get to the point where we could implement this in a way that is best for everyone.

The one thing that we keep coming back to is that this is really healthcare equality. By doing sequencing, we don't exclude anyone who can't afford it, who has to pay out of pocket, whose insurance won't cover it. The information at the time of the referral may help in the management of these children, as well.

So the molecular subcommittee, the mission was to ensure continuity and the responsible growth of emerging technologies in the newborn screening and public health environment. Several states have had or have representatives of this -- on the subcommittee over the years. We met informally in 2010 for the first time as just a group -- as a forum group, and we became an official subcommittee in 2011, at the newborn screening symposium. There's a lot of objectives up here for you to read, but basically, what we try to do is foster a collaborative and educational environment. We involve laboratories, newborn screening programs, and the CDC and APHL. We act in a cooperative way, and we basically are a provider of assistance and resources to anyone who's interested in implementing molecular technology in a newborn screening program.

This timeline shows sort of where we started and where we are. One of our activities is to hold an annual molecular workshop down at the CDC each year. Every year, we get more

applications than we can accept in the program, so we know molecular is on the minds of many state laboratories. We have -- they're informal assessments or formal assessments, but not a regulatory assessment, of programs. We call them MAP visits, Molecular Assessment Program.

And we have a new leader, as of 2016, Dr. Rachel Lee took over for me. She's from the Texas screening program. She's the new chair. Right now, we've done going on 19 or 20 MAP visits since they began back in 2012, I believe.

So this just lists some of the things that we have done, as I said, the workshops, the assessment program. We have a website on the APHL website, where you can go and look at different resources about different tests. There's slide sets up there and webinars that have been held over the years. We've created a paradigm for newborn screening molecular pilots and worked with the NIH on that, and we've made many presentations to the newborn screening community and the genetics community, also, about the goals of what we do.

We're in the process, right now, of planning a gene sequencing meeting to look at the current status of sequencing in newborn screening, looking at the lab and the follow up, which are both important parts of the program. That's targeted to occur in the first quarter of 2017, and t's going to involve newborn screening lab and follow-up managers as a first start. If you have questions, you can talk to Laura, she's in the audience back there somewhere -- from APHL, and Suzanne Cordovado at CDC. Also, Rachel is helping with that as well.

We're also getting ready to launch a second molecular survey. We originally did one back in 2010 to send out to find out the status of testing in laboratories across the country. Six years have gone. The field has changed quite a bit. It's time to take another look and see what states are planning to do, what they're going to need for quality assurance and quality control, what platforms are being used, and what testing is being planned. And again, you can contact Laura or Suzanne if you need some more information on

that, but that's hopefully being launched sometime this fall.

So that's what we've been working on, as a community, with APHL. There's many other people that I'd like to thank for help with some of the slides or data, and the support of my own laboratory, Dr. Jill Taylor, in our entre into next-gen sequencing. And so, thank you for your attention.

(Applause.)

CHAIR BOCCHINI: Thank you, Michele, for an excellent presentation.

DR. CAGGANA: Thank you.

CHAIR BOCCHINI: It was state of the art, where we are and where we're going. Let's open this for questions or comments from the committee. Carol?

DR. GREENE: Terrific presentation, thank you. And also --

DR. CAGGANA: Appreciate it.

DR. GREENE: -- some great, great work going on. You mentioned, but obviously can't

solve, all the questions about the personnel that's needed, because doing that analysis requires knowledge of a very changing literature, but clearly that's something that's going to be looked at. I have -- and also cost, you were looking at.

I have a very practical question. For CF, where the mutations are so well known, and you've got the very high IRT group and you're changing the protocol, a practical clinical question. So, you're going to find -- using the sequencing, you're going to find most babies. You've got it up to 98 point something percent, but it's still not 100 percent.

DR. CAGGANA: Correct.

DR. GREENE: So it increases the specificity, and it actually decreases the sensitivity. Because if you went with the IRT alone, you've got a much higher false positive rate, but I think it's a little bit of misleading -- and you didn't actually say it, but I don't think it increases the sensitivity. It decreases the sensitivity, unless you're planning

to follow up the very high IRT independently.

And I have one other caveat, and that is 98 percent times 98 percent is the chance that -- 98.2 times 98.2 is the chance that you're going to find two mutations and then you're going to find the ones with the one and you're going to sequence them and so you're going to sweat chloride on them, and then you've only got the tiny chance of missing both mutations, assuming they're not consanguineous, in which case you only had one chance at the mutation. Do you screen first to find out if it's a consanguineous family, in which case your chances of missing the mutation is actually the 2 percent?

DR. CAGGANA: We don't -- the answer to your second question is no. What I left off of this is we also are running a series of supplemental assays. I took it out for time and just explanation, but we're also looking at several common dilution tests as well.

So they're going to be done in concert with the sequencing, and so the sensitivity to

where we, you know -- presumably, we talk to our CF providers and they can live with the fact that we may miss -- we're going to miss a couple babies. But we're also looking at the common dilutions, and a couple that we actually found more than once in our population in New York.

DR. GREENE: And I think that's -- not saying there's anything bad about this, it's just that it's screening, and screening is not necessarily going to be perfect, but it is not necessarily true to say DNA increases the sensitivity in all cases, especially when you have, in this case maybe an overly sensitive functional test. Because you had a more sensitive test --

DR. CAGGANA: Right.

DR. GREENE: -- and you're making it more specific. And the deletion will help, but the question about consanguinity still stands because there's people who are going to have regulatory gene mutations.

MEMBER BAKER: Michele, I would -- when we do the CF, you have two tiers. You use RT first,

then DNA. It doesn't matter, you do small panel and the whole gene. I think largely, sensitivity hasn't declined because if on first tier, you did not pick it up, then --

DR. CAGGANA: You miss more that way.

MEMBER BAKER: My understanding, from our state's experience, our sensitivity is 96 percent. The idea is, can we decrease the cutoff to increase sensitivity? But the hesitation is you will pick up more carrier. But I think that's an opportunity here now, yes, if your state could go in increment, only have two mutations, you would recommend to do the sweat test.

I think you're in a good position to say, hey, we can decrease IRT level. That way it truly increases sensitivity. My understanding is -- I think our experience, actually, the 96 percent sensitivity largely is because the cases, true cases, didn't meet our IRT cutoff. I do believe this is largely other states' experience.

DR. CAGGANA: Yes, and we did look at that. We looked at changing -- you know, how many

babies would we need to test if we made it the top 94 percent or 93 percent? How many more would we send? Then if we brought it down such that we only looked at the top 4 percent by DNA, the babies that we've missed on IRT are quite low. Their IRTs are quite low. We actually are part of the study of Dr. Kharrazi, in California, of looking at these babies who screen negative, but have CF. It kind of works from both directions.

DR. GREENE: Not to get too technical, but part of the issue is the 96 percent is just the 4 percent with the meconium ileus, they have the extremely low IRT. You'd have to -- I mean they don't have a high IRT. You'd have to drop your cutoff way down, and you'd functionally be doing DNA tests.

DR. CAGGANA: Our providers have increasingly been telling us that the baby has meconium so that we do DNA regardless of IRT.

MEMBER BAKER: Just a very quick -- that's actually leading a point I would like to make. If we really use genetic testing to

increase the performance, I think a CFTR gene maybe is a good example, are we in a position to think about genetic testing as a first tier?

CHAIR BOCCHINI: Before the next comment, just to remind everybody, please state your name before you speak, and then we're hearing that some people in the back and some people on the phone can't hear, so please get close to the microphone when you speak. Joan?

MEMBER SCOTT: Thank you very much for that presentation. And so for Michele, or maybe other public health folk who are represented around the table, what I also think I'm hearing you say is there's a great variability across public health laboratory systems to move in this technology, or no?

You guys are leaders. There are a few other states that are doing a lot in this area. Can you give a brush -- sort of broad brushes about the overall capacity or capabilities across the United States?

DR. CAGGANA: Most labs, I think we're

up to about, is it 43 or 4 -- where's Carla? Do you know offhand? It's around there doing SCID. Are any of the new steps folks in the back? So there is that element of extracting DNA from a blood spot and the labs that are screening for SCID are halfway there because they have that part set up.

What we've found is a lot of programs don't have a molecular lab dedicated to newborn screening. They have a molecular lab in the public health program, and they're the ones that are assisting, so there's that element. There's workflow and space elements in some programs. Off the top of my head, I don't know the number of states doing CF DNA, but it's a fair number. I don't think there's too too many doing just IRT/IRG anymore.

So there's that basis, but it's like taking that leap from doing the targeted panels to the sequencing where there's work to be done. There's very few programs that are doing the sequencing piece.

MEMBER BAKER: Also I will -- adding on that, Michele described, even you do some

sequencing but next gen --

DR. CAGGANA: Big jump.

MEMBER BAKER: -- is quite a step to take.

DR. CAGGANA: It's a big jump.

MEMBER BAKER: Yes. And we are currently using next gen to do the CFTR, but for the interest in time, I won't get into details, and the why is the turnaround time. Michele mentioned that, and I want to emphasize that.

Because if you seek the whole next gen, really, actually it's effective because you get more mutations and with short time, but think about -- newborn screening timeline is going to be challenging. That's is one part. But I feel it's always -- go back with any items we discuss, you think about it, what's the purpose, what'd you gain, and what'd you lose, the pro and cons?

For CF, I think it's a very good example. Michele mentioned that. I want to emphasize you get a positive screening result to a physician, you really now allow them to schedule a sweat test in

a few weeks' age. So we have been discussing, our state, in terms of pick the method. We made a conscious decision, said we'd rather have a better -- more information, than say, give me five days.

That's the decision we made. Secondly is the charging, for us, I think we're a small state, is the cost is still an issue. The next gen sequencing, compared with the conventional method, you test the one sample almost at the same cost you test 40 samples because the flow cells, you use, you are done. With one state, you have to think about the cost. And the interesting thing is sometimes this kind of thing makes me think about multiple state together may make the cost more reasonable.

MEMBER CUTHBERT: Carla Cuthbert. To address more of what you were asking, Joan, the survey that Michele was talking about is truly to get another assessment of where all of the states are. This was done in 2010 and coincided in and around the formation of the steering committee, which eventually became the APHL Newborn Screening

Molecular Subcommittee. And so because we are at such a different place with things happening with NIH and their newborn screening grants, we wanted to be able to get an assessment of where the states currently are. For CDC, we would like to know what the needs are, specifically how we should prioritize our own resources.

I always keep looking at the molecular -- the training group that happens every year. And yes, there is a bigger need. We have very good teachers of that course, and we're looking to see, again -- I know Suzanne is probably hearing this, doesn't want me to say it, we're looking to see whether or not we need to have two courses in that year, but there is a big need, and we want to get an assessment of where they are.

There are some groups, in some states, who are a little further ahead, others who are not. We just want to make sure that we can help elevate the entire group as we're thinking about it. That's where we want to go as well with the sequencing discussion. It's not about everything

that is happening currently. We want to educate those who are not as well informed and just let them know what sort of options they've got, and so on, and just hear from them, in terms of laboratory and in follow up.

MEMBER TARINI: Beth Tarini. I want to follow up on Mei's point that in the spirit of reconsidering, at some point, our previous recommendations, that it is possible that as this moves forward across other states' programs, that the states take a hit on a quality improvement metric of all tests reported by seven days.

So that could be a disincentive, especially if someone from the outside looks at this and says, oh, you're not meeting your metrics. Your metrics, set by the Secretary of HHS, are agreed upon that all tests -- because all newborn screening -- I'm looking at it now. All newborn screening tests completed within seven days -- it's all, not just the time critical. So we should keep that in mind, that we, in our past recommendations, don't hinder the potential innovation that could

be going on here.

DR. WATSON: We actually -- or I already had initial discussions with Michele about the ultimate problem, which is the difference between the analytical sensitivities in using next gen sequencing versus interpreting variants, and it's clear that there is an incredibly long tale of variants that are only seen once or twice in most any gene we've looked at.

As this shifts into the newborn screening labs, I think one of the things that's going to be most helpful is going to -- because most of the labs won't have people who are board certified in molecular diagnostics, which gets you better able to deal with interpreting variants and classifying them appropriately -- is going to be increasing data sharing and out of public health labs, hopefully, because if you're going to be the primary source of mutation testing, which your state already is in the LSDs, getting that into ClinVar, where we will have much more curated data about the pathogenicity of variants, can only help

the states get more and more involved because it'll greatly simplify the interpretation of results that are uncommon or rare variants.

So I think -- I don't know how many other states are where you and Mei's are in this, but I organize the metabolic group for ClinGen and some of the other groups that are organizing around specialty areas on variant interpretation and would be happy to work with you all in figuring out how do we involve the state programs in this, because you're going to have a lot of data that can only improve interpretation in the long term.

DR. CAGGANA: Right. The caveat that we need to make sure that we take into account is that we need to close the loop on the diagnosis and the sort of long term, and that's a whole other spin around the wheel for that.

DR. WATSON: No doubt. You probably have the rare luxury -- CFTR did functional testing of variants after the fact. You actually start with patients who have functionally demonstrated that something isn't working and can now interpret

the variants around that.

DR. CAGGANA: Yes.

MEMBER MATERN: Just quickly, to totally agree with Michele here that one has to be very careful to entering the newborn screening genotypes, or just the variants, into ClinVar or anywhere else because we just don't know. If you look at the Krabbe experience, if all of those variants were in ClinVar, I think there would be even more confusion about what Krabbe disease is. Among all of those, there are only five cases in the first nine years that should have been entered.

I think I would also prefer not to see the variants. They're nice, but I want to know the genotypes that are making you sick, and not the variants, the pathogenic variants that, in combination with another variant may, in the end, mean nothing. Genotypes of certain significance is what I would like to see, and not variants and genotypes of uncertain significance.

DR. WATSON: It's not until we collect enough that we move them from uncertainty into

other categories, so, you know, it's a trade-off. We do have to collect it all and then we have to curate it to get rid of that which isn't significant.

CHAIR BOCCHINI: All right, with that, I want to thank Dr. Caggana for an excellent presentation, good discussion and I want to close the morning session to give people a chance to have lunch. We're going to get back here promptly at 1:00 to start the afternoon meeting, so thank you.

(Whereupon, the above-entitled meeting went off the record at 12:14 p.m. and resumed at 1:05 p.m.)

CHAIR BOCCHINI: All right, let's go ahead and get this afternoon session started. We need to begin with a roll call for attendance. Quickly, Don Bailey?

MEMBER BAILEY: Here.

CHAIR BOCCHINI: I'm here. Mei?

MEMBER BAKER: Here.

CHAIR BOCCHINI: Jeff?

MEMBER BROSCO: Here.

CHAIR BOCCHINI: Carla Cuthbert?

MEMBER CUTHBERT: Here.

CHAIR BOCCHINI: Kellie Kelm?

MEMBER KELM: Here.

CHAIR BOCCHINI: Fred is not back yet. Dieter?

MEMBER MATERN: Here.

CHAIR BOCCHINI: Steve McDonough?

MEMBER MCDONOUGH: Here.

CHAIR BOCCHINI: Mistry is not going to be available to us this afternoon. Melissa Parisi?

MEMBER PARISI: Here.

CHAIR BOCCHINI: Annamarie Saarinen?

MEMBER SAARINEN: Here.

CHAIR BOCCHINI: Joan Scott?

MEMBER SCOTT: Here.

CHAIR BOCCHINI: Beth Tarini?

MEMBER TARINI: Here.

CHAIR BOCCHINI: Cathy Wicklund?

MEMBER WICKLUND: Here.

CHAIR BOCCHINI: And Debi Sarkar.

MS. SARKAR: Here.

CHAIR BOCCHINI: Bob Ostrander?

DR. OSTRANDER: Here.

CHAIR BOCCHINI: Mike Watson?

DR. WATSON: Here.

CHAIR BOCCHINI: Joseph Biggio on the phone? Susan Tanksley?

DR. TANKSLEY: Here.

CHAIR BOCCHINI: Chris Kus on the phone?

DR. KUS: Here.

CHAIR BOCCHINI: Thank you. Adam Kanis on the phone?

DR. KANIS: Here.

CHAIR BOCCHINI: Great. Natasha Bonhomme?

MS. BONHOMME: Here.

CHAIR BOCCHINI: Siobhan Dolan?

DR. DOLAN: Here.

CHAIR BOCCHINI: Cate Vockley?

MS. VOCKLEY: Here.

CHAIR BOCCHINI: And Carol Greene?

Okay. So this afternoon we have a panel presentation. This is from the Newborn Screening and Genomic Medicine and Public Health grantees. Don Bailey has agreed to lead this discussion. They will begin with a panel discussion. I'm going to ask him to introduce our four panelists, and then following the panel discussion, we'll have an open committee discussion with the panelists. Don, we'll let you get started. Thank you.

MEMBER BAILEY: Great, thank you, Dr. Bocchini. We appreciate the opportunity to share information about these four centers.

So speaking on behalf of a large number of individuals who are participating in these centers, we'll mention a few of them here today, but so it's a cast of -- it takes a village for us to do this kind of work.

My job is to basically tee this up, give you a little bit of background and information about how this got started and what are the overarching goals of the program, and then we'll

have one representative from each of the four funded centers to talk with us about -- give us a very quick overview of what their center is doing. Then I've asked them to highlight one interesting finding or process or case study or something about lessons learned so far from our activities.

We have a cute name, NSIGHT, Newborn Sequencing in Genomic Medicine and Public Health. It's very different from what Michele, Dr. Caggana talked about this morning, and I appreciate that introduction very much. That was a great background and introduction to what we're doing here. We really haven't been focusing as much on newborn screening as opposed to using sequencing with newborns in a variety of different contexts. And I'll share some of that information with you very shortly.

This effort is co-funded by NICHD, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Human Genome Research Institute.

I just want to give a shout out to, first

of all, Anastasia Wise. Anastasia, I saw you back there somewhere, raise your hand. Dr. Wise is from NHGRI. She's been the lead person from that institute helping to coordinate and push this. I'll describe some of those activities in a minute. Then Dr. Tiina Urv, who was at NICHD and is now at the National Center for Advancing Translational Science, was the primary contact person from NICHD. They both have been tremendous in helping push us forward more collectively as a group.

Dr. Parisi is now the person who's primarily representing NICHD in that initiative. Let me see here. As you know from our discussion this morning, as well as other days in this committee, newborn screening is an evolving public health program that's constantly faced with new challenges and new opportunities. How's that for a nice way to describe it?

We've got all these things that are going on. We've written about it in this one article, but a lot of people have written about them. We've got advanced understanding of the

causes of diseases and treatments. We have challenges we're facing as a committee and getting evidence for pre-symptomatic treatment of rare disorders. We have advocates coming every meeting and pushing us for expanded screening for their child's condition. We've got state labs that have limited state budgets. Those budgets often compromise their capacity for doing everything they would like to do, in terms of screening and follow up. And then mainly the focus of our talk today is new technologies for screening, including maybe the eventual possibility of whole genome or whole exome sequencing at some point in the future.

The history of change, paradigm shifts in a field, often means that there's some disruption that comes in and completely changes things. You're not really expecting it, and you haven't done the preparatory work to get ready for it. Fortunately, we've not been in that case with whole genome and whole exome sequencing.

People have been talking about this for a number of years, so we now have the opportunity

to do anticipatory research. Some people have said, "These centers are all about pushing sequencing and newborn screening." That's not what the centers are about. They're about studying the potential ramifications of sequencing in the newborn period and what might be some possible uses of them. In this process -- I appreciate Tiina Urv sharing several slides with me. In 2010, NIH held a meeting on newborn screening in the genomic area. They brought in experts from academia, from industry, from federal agencies, in a variety of fields of newborn screening and genomics, and talked about this issue, said what should we do about it?

The subtitle is setting the research agenda. The outcomes of this meeting were really three-fold. It's really important to evaluate genomic data in newborns, in using newborn screening potentially as a framework, but it's also important to prioritize clinical validity and clinical utility, not just analytical validity, and it's important to address ethical, legal, and

social concerns.

In parallel with that meeting, there have been quite a few articles that have come out about sequencing of newborns and babies, a lot of them written by people around this table or in this room. You can look through this and see a lot of co-authors or authors. You can see these titles reflect some of the questions and concerns that people have had, variants of uncertain significance in newborn screening disorders, implications for large-scale sequencing. Most of them talk about the challenges, the challenges of using next-generation sequencing, genetic professionals' opinions about whole genome sequencing, what are parents' views about sequencing, ethical issues, etc. There's been quite a bit of discussion of this in the literature.

This discussion has been robust. It's been important. It needs to continue, and there need to be data as a part of the discussion. That's what the primary goal of these centers is. NIH issued an RFA in 2012 called Genomic Sequencing in

Newborn Screening Disorders. This was a U19 grant. Those of you who are aware of this, it's a cooperative agreement.

Under a cooperative agreement mechanism, there's a lot of interaction with the agencies that are funding this. That turned out to be the case. As a result of this -- in the RFA, the Centers were required to address one or more of the following questions. One question is for disorders currently screened in newborns, how can genomic sequencing replicate or augment known newborn screening results? Dr. Caggana gave some great examples of that today. Secondly, what knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide? Third, what additional clinical information could be learned from genomic sequencing, relevant to clinical care of newborns, even if it's not in the context of newborn screening?

Each center had to address at least one of these topics in their proposal. In addition,

each center was required to have three components, a sequencing component, of course, a clinical research component, which would be, obviously, identifying and following up babies who were identified as a part of sequencing, and then an ethical, legal, and social implications component.

Each center had to have these three components built into its application. I got involved with this because I worked with Dr. Cindy Powell and the team at UNC. I've been leading, along with a group of people in my shop, the ELSI component of our proposal. There were four awardees, Brigham and Women's Hospital in Boston, Children's Mercy Hospital in Kansas City, and now at Rady Children's Hospital in San Diego, University of California, San Francisco, and then UNC, Chapel Hill. From Brigham and Women's Hospital, Dr. Robert Green will be presenting today; from Rady Children's, we have Dr. David Dimmock; from the University of California, San Francisco, Barbara Koenig; and then Cindy Powell from UNC Chapel Hill.

Again, each of these groups have a large number of investigators. We actually have an article I'll describe in a minute talking about the collective network. We have a very long list of co-authors on the paper. These centers were not originally funded as a network. It's a competition.

We were competing against others and other applicants, so we couldn't really propose collaborative activities with each other in our applications, but through the cooperative agreement mechanism, NICH and NHGRI have provided quite a bit of support and encouragement for cross-center interactions and collaborations, when appropriate. Again, I credit Dr. Urv and Dr. Wise for really pushing and helping, in a positive way, to help make this happen. For example, we now have bi-weekly conference calls of all investigators. We have working groups on ethical issues and common data elements. We have an annual meeting of Center investigators to share findings and challenges. We have other meetings

coordinated with conferences on related topics.

If a core group of our investigators are at a certain meeting, we'll get together then. John Lantos, who is at Children's Mercy, edited a special issue -- a supplement to Pediatrics recently on ethical issues in genomic testing of children. Most of the articles in that issue were authored by people in this network.

We have a jointly authored marker paper, led by Jonathan Berg, at the University of North Carolina -- that's one of many, many authors, as I mentioned earlier -- describing center activities. It's been -- I think I'm allowed to say this has been provisionally accepted for publication in Pediatrics, pending minor revisions. The goals for today, as I mentioned, are for us to give a very brief overview of each of the funded centers, and mainly to focus our time on giving examples of a finding or a process that would be of interest to the committee, and then allow time for questions and discussion by committee members and organizational

representatives. We're not going to do Q&A after each center's presentation.

I think that would -- even though I'm sure there will be questions coming up after each one of them, we want to make sure we have sufficient time for the four presentations, after which we'll have hopefully about a half an hour left for discussion and questions across the four centers. With that, I'm going to turn it over to Dr. Powell from the -- I'm not going to introduce -- read the bios and so forth.

Those are in the briefing book. People can talk about themselves if they'd like to, but I think they mostly want to talk about the data and what they're doing. I will need help in finding the next presentation.

DR. POWELL: Thank you. Good afternoon. Our various projects are sort of divided into two main areas. One is looking at the use of next-generation sequencing in critically ill newborns or newborns with serious conditions. Then other groups have looked at its use in newborn

screening, more in the potential for public health benefits. Some groups combine those two things. Our group is really focused more on the potential use in following up in children who have conditions identified through newborn screening, as well as looking at what this technology may be able to lead us to in the future in terms of expansion.

If we think a little bit about the history of newborn screening, a lot of it has really been industry driven and technology driven. If you think about, initially, when Dr. Guthrie developed the bacterial inhibition assay to detect phenylketonuria, this went on.

Certainly, when Dr. David Millington realized that tandem mass spectrometry could be used in looking at inborn errors of metabolism and detecting that and the potential to use that on a wide-scale basis for screening newborns. And then this led to Dr. Howell/Dr. Watson convening their committee to really break down what were the conditions that were best to look for in newborns and utilize in newborn screening? And that led to

the 29 initial core conditions and 25 secondary targets for universal newborn screening. Now, with the advent of next-generation sequencing or massively parallel sequencing, this has the potential to exponentially increase the numbers of conditions that we could detect in newborn screening.

One of the big challenges is to figure out how we can be good stewards of that information and where can we really utilize this information in a beneficial way? You've heard from Dr. Caggana about next-generation sequencing. I use this as a way to differentiate between, I think, what, currently, some of the state newborn screening labs are using it for, and then some of what we're looking at it from a research basis for potential use.

Basically, you have a patient. You collect a sample, whether it's their dried blood sample or a saliva sample. You extract DNA from that sample, and then you can prepare that sample using a library of what you are interested in

looking at. If you were just interested in looking at the CFTR cystic fibrosis gene, you would do a capture to just sequence that one specific gene, or you might want to do a panel of genes, for example. You can think about that as a targeted sequencing method. Then you do your sequencing, utilizing what's now just a very small piece of equipment on a desktop, but a big part of it is the analysis part.

The bioinformatics and computing part of this represents a huge component of utilizing next-generation sequencing. But if you were to do either a whole genome screen or sequencing or whole exome sequencing, as is done commercially now, you could just target what that analysis gives you. Even though you might be looking at every known gene, you could just ask your computer system to give you the information that you're interested in looking at.

I'll refer to that as targeted analysis. There's still a lot of human time that needs to go into it to figure out what's a

significant variation or mutation in a gene, and what's just a common variant, just a population or familial variant. We'll be talking about this. In order to figure out what genes we should look at, if we're going to do exome sequencing, we have what we call our binning committee at University of North Carolina. This is comprised of clinical geneticists, biochemical geneticists, genetic counselors, metabolic dieticians, molecular geneticists and experts, and a lot of our students and post-docs are included in that. We use a semi-quantitative metric to score gene disease pairs, using a 0 to 3 point scale.

This is basically a very mini evidence-based review, nothing similar to the much more in-depth evidence-based review that's done by this committee and Dr. Kemper. We look at the severity of a disease, meaning what's the effect on morbidity or mortality in an individual carrying a pathogenic, so a known mutation in that gene? Is there modest or no effect?

Is it serious or chronic morbidity?

Could it lead to possible death or severe intellectual disability, or is it associated with sudden death or unavoidable death in childhood? We look at the likelihood of that outcome, what's the chance that the problem will materialize? In essence, what's the penetrance of that genetic disorder? Is it very low? Is it 5 percent? Is it 50 percent or higher? Then what's the efficacy? Do we have any intervention if one does have a pathogenic variant? How effective are those interventions in preventing harm? Is there no effective intervention? Is it minimally/modestly/highly effective? Then what's the acceptability of that intervention, whether it's a special diet that someone would be required to be on?

Is it monitoring, like with ultrasounds or a colonoscopy, or is it much more invasive, requiring a surgical procedure, let's say? Is it minimally up to highly acceptable for that intervention? Then what's the knowledge base?

There are many gene disease pairs that

are out there, but may have only been described in one family, an in-bred family in the other side of the world, or is there a lot of evidence base for this gene, and are there even practice guidelines available for how to take care of those patients? We use this scoring system. I'll give you an example of a condition that I think most of you are familiar with, PKU, phenylketonuria, due to mutations in the phenylalanine hydroxylase gene. The severity of disease leading to severe intellectual disability if untreated got a score of 2. The likelihood, again, if someone's not treated, a 3, a high likelihood. The effectiveness, we know we have very effective interventions, so that got a 3. The acceptability, while it's not the easiest thing to be on a low-protein diet and drinking formula, it's not one of the worst things to do, so that got a score of 2, and there's an excellent knowledge base about that, so that got a total score of 13.

Looking at one of the potential candidate conditions for what we're calling a

next-generation sequencing newborn screen is something called multiple endocrine neoplasia. There's several different forms. This one is Type 2B.

It's associated with very early onset thyroid cancer that can begin in the newborn period or infancy. Usually, by the time it's detected, there's already significant metastatic disease. There's 100 percent penetrance for many of the known pathogenic mutations within this gene. It can also lead to another type of tumor, called a pheochromocytoma, but that's only in about 50 percent of patients. Other features, including the growth of some little lesions in the mucous membranes and change in body habitus, described as a marfanoid or Marfan syndrome-like body habitus, but those really aren't obvious until an individual is older, like adolescence or early adulthood, so you're not going to pick it up, otherwise, in a newborn.

In the scoring, it got a severity score of 2, likelihood of severe outcome 3. We know that

for some of these mutations, there's complete penetrance. There's good interventions. You can begin early ultrasound of the thyroid. If there's any suspicious lesions, you can remove the thyroid gland. Again, acceptability got a 2, in terms of the screening for this, and our knowledge base is quite good.

That received a similar score of 13. Going on, just one more example, Long QT syndrome is associated with some cases of sudden infant death, so SIDS deaths. It also can be associated with later unexplained sudden death in older individuals. It got a score of 3 for the severity, 2 for the likelihood. We know that some people can have a variance or mutations in the gene, but never have any problems, but you can do EKGs to pick up whether there is this long QT in the EKG analysis. So there's effective interventions, acceptable interventions, and the knowledge base for that was a 3, so that also got a score of 13. There are now 15,350 human genes in Online Mendelian Inheritance in Man. There are 4,800 genes in OMIM with a

phenotypic description and a known molecular basis.

So far in our project, we've scored 790 of these gene condition pairs, and I wanted to share with you how those are broken down so far. We have concentrated more on the childhood onset. If you look at the table here, we have an actionability score. Is something actionable? Can we take medical action to either prevent complications or detect things early, or is it lower actionability, and the age of onset from infancy/childhood to adulthood.

So far, in the childhood onset, medically actionable conditions, there are 307 that scored in that category, including those already on the RUS, and others, such as I mentioned with the multiple endocrine neoplasia and one for familial adenomatous polyposis, which causes risk of liver tumors and early colon cancer. Then WT1 gene, associated with a condition called Denys-Drash syndrome, which may lead to hypospadias, and then a risk of Wilms tumor, a tumor

of the kidney.

There are conditions where you can't really say they may have onset in childhood or adulthood, some of the long QT syndromes, some of the cardiomyopathy conditions, so things, potentially, that could lead to a high school athlete on the football team who suddenly drops dead from a cardiac arrest due to a cardiomyopathy.

Then there are those that don't have onset until adulthood, such as the breast cancer genes and colon cancer genes. Then we have a list of conditions that have pediatric onset, but for which, at least so far, there's no good way to intervene.

However, some may argue that just knowledge of the condition may be helpful for people to avoid that diagnostic odyssey that we've heard about today. That would include things like Rett syndrome, and Krabbe is where we put that one. Then there's these non-actionable adult onset conditions that I'll talk briefly about. I wanted to give you a couple more slides on what we're

doing. I'll just talk about it. We have a group of patients with known conditions that were picked up through traditional newborn screening, such as PKU, MCAD. We're going to be looking at whether, with whole exome sequencing, we're able to detect those conditions on a molecular basis.

Then we also have a group of what we call our healthy newborn cohort, whose mothers and fathers are being recruited from our prenatal clinic at our hospital, although those children, hopefully, will not have any significant conditions, but we're very interested in how people make decisions about whether or not they want their child sequenced, what type of conditions do they want to know about?

We will have two groups; one group of parents will be able to make decisions about what additional information they want. Do they want to learn about the adult onset conditions, carrier status, non-actionable childhood onset conditions? We'll only analyze the information if parents want to get that information back. With

our partners at RTI and Dr. Bailey and his group, we've developed a decision aid tool that helps parents to decide what kind of information they're interested in getting. I'd like to thank my team, and Dr. Jonathan Berg is my co-PI on this project.

MEMBER BAILEY: Thank you, Cindy. I know you've probably got a lot of questions and comments already, but we're going to move forward, so Dr. Dimmock is going to be next.

DR. DIMMOCK: I'm pleased to be able to be invited to come and talk to you guys about some of the fun that we've been having in Kansas City and in San Diego over the last couple of years. My disclaimer is that I basically did none of this work, so I'm presenting other people's work.

Our genomic institute in San Diego was started just over a year ago, with a $120 million gift. Our focus is on implementation science of precision medicine, actually generating evidence of precision medicine itself, in the context of a learning healthcare system. There's a lot of jargon. Our primary focus is Rady Children's

Hospital, our tertiary quaternary care hospital. Many of you may not realize, but 14 percent of U.S. newborns end up being admitted to a neonatal intensive care unit. This is a huge number of kids, and it's a huge burden of care. Speaking as a parent of two NICU graduates, it's actually quite a stressful place to be, as well. We think that infants are the logical initial focus to precision medicine.

There are 8,000 known genetic diseases. It's a very big number. These actually affect just over 3 percent of U.S. children. I would like to remind the committee that there is a C on the end of the committee's name for children. They are the leading cause of death in infants, and it is also the leading cause of death in pediatric intensive care units and in pediatric neonatal intensive care units.

From our understanding the background and making diagnosis, presentation is less confounded by the environment. It's not a 50-year-old chain smoker who you've got to look at

what's going on, although Zika is causing us a lot of entertainment right now. The other big deal with infants -- and I don't have to persuade many people sitting around this table -- is you can make 80 years of benefit with one case. We're kind of proud of our world record for the fastest genome. That's kind of a nice abstract. I actually want to walk you through a case. This case was actually sequenced in Kansas City. This was a baby that presented in acute liver failure. We're going to start a countdown clock. This baby is admitted to the ICU.

One of the biggest challenges, as most people will understanding, in doing a research project, is actually getting consent. It's often, for us, the most time-consuming part of sequencing a genome. It can take two or three days to get consent. This case wasn't like that. Time 0, we actually managed to get Mom and Dad and the baby's blood all at once, once again, not a small feat.

Within two minutes, we had the sample at our institute. Within an hour, we had isolated

the DNA. Preparing the DNA in what's called a library preparation, to make it ready to go into the sequencer, right now takes us about five hours. We have some new ways of shaving some time off of this. We used a highly souped-up, specialized, personalized genome sequencer that is being customized for us by Illumina, with proprietary software and with different flow cells, which allows us to get DNA data, from the time the blood is drawn to actually having the data off of the sequencer in just around 24 hours. You've got 120 billion ladders -- yes, I said "B" with a billion.

You've got to go from that to actually making a diagnosis. You get 2.8 billion calls. Anyone want to think about how big a number that is, or how long it would take you to look at them one by one? Actually, in this case, we had just over 5 million variants from what's called the reference sequence, which is sort of a collection of a bunch of random people who gave DNA for the original genome sequencing project.

Actually, you can estimate the

background of this child by the fact that it's only 5 million variants. If we trim this down to a half percent frequency, because this is a rare disease, after all, we can ignore things that are around and found in 1 in 100 people. We get down to 1.3 million variants. That is still a huge, huge number. We have some proprietary algorithms that allow us to predict whether or not this is likely to cause disease. We're not just talking about coding region variants here. We're talking about transcription binding factors. We're talking about deep intronic splice variants and gain of function variants, as well as loss of function variants.

I would argue that the biggest challenge right now, today, for us, with diagnosis, delivery of -- making a diagnosis based on a clinical presentation is actually making sense of what is the clinical presentation. We are working on processes to actually automatically pull this from the electronic medical record.

Anyone who's read a doctor's note will

know that is not a small feat. In the meantime, we're actually hand abstracting from the clinical notes. In this child's case, we went from the 8,000 number, or actually probably more like about 6,000 that we have in the database, down to 341 possible diagnoses that could explain this child's problems. That's still a very big number. If you want to hand look at all of the variants that form those 341 genes, you're going to spend a long time doing it. There were a few things that were on this list that were kind of interesting, like fetal liver failure in infancy, so not very helpful to them. There was one particular term that stuck out, which I'm just going to call it HLH because it's such a mouthful. That actually was the diagnosis in this child. So 25 hours and 43 minutes after getting consent, we had a diagnosis.

This child had two variants in a gene called perforin-1, a likely pathogenic variant, which has been supported by case control studies, and a definitely pathogenic variant, once again supported by functional as well as case control

studies. So this child has HLH Type 2. The very good news is there is treatment for it. Having started treatment, within seven days, this child's bleeding problems had fully resolved.

This child is now 36 months old. His liver's working just fine. We've saved about 80 quality-adjusted life years with one case. I could give you case stories all day about this kid and that kid and one kid and the other kid, but as everyone here knows, there's a lot of kids in the U.S. -- 4 million born a year -- so can we scale this up? In the first 115 babies that were sequenced at Kansas City and Rady in the NSIGHT program, we achieved a 57 percent diagnosis rate. This is really a phenomenal number. Does it make a difference? You can make a diagnosis. You can put a label on it. It actually does change care. In approximately a third of cases where we made a diagnosis, we changed care.

Interestingly, and perhaps challengingly, the most common way that we changed care is by deciding that this child had a fatal

diagnosis and we were going to move to a palliative comfort care route. This is one of the things we don't talk a lot about with genome sequencing, but this is a very common outcome when we sequence very sick children.

It is one of the things we have to be ready for, both emotionally, ourselves, and when we present the opportunity of testing to families. We can tell you the happy ever after stories, and I'm going to argue that these six are actually happy ever after stories, as well, in one sense, because it allowed the parents to spend time with their children and not do heroics that would hurt the child, but not help them. In three of our kids, we avoided very significant health problems by knowing diagnosis ahead of time. I've already presented the one case, where we really made a huge difference and saved the child's life. We have a ten-year vision at Rady. And our vision is actually not just Southern California, but I want to talk about Southern California first.

There is almost 3.3 million people that

live in San Diego county, which is the little bit at the bottom, on the border. About 75 percent of the patients in our children's hospital are from under-represented or minority groups. You guys may not realize this, but less than 3 percent of people in clinical trials right now are from under-represented minorities. The reference genome does not take this into account, and we have very limited data on individuals that are under-represented.

We have a huge task ahead of us. However, if you want to get an idea of how big our problem in San Diego County is, our estimates right now are -- very conservatively -- that there are 22,000 young children with genetic diseases that are undiagnosed. We estimate that within the next five years, we're going to be able to sequence about 8,000 genomes a year. To give you guys an idea of how big a challenge that is, we went live with sequencing in San Diego a month ago, and we've only managed to do 26 genomes. This requires a big change. Doing 8,000 genomes a year will lead to

1,320 some new diagnoses a year and will save around 5,000 quality adjusted life years. That's a really big number.

Our ten-year vision is for San Diego, Imperial and Riverside Counties, and with our sister hospital in Orange County. We estimate here that we're going to be looking to do 24,000 genomes a year, making around 4,000 diagnoses a year, and saving around 16,000 qualities. But if all we did was save the babies in San Diego, we'd only be helping 3,000 or 4,000 kids a year.

Our vision is much bigger than that. We want to provide the evidence that genomic medicine makes a difference, or doesn't, and we want to understand how one implements it. The babies are waiting, and we're very excited to make a change and to generate the evidence that shows what this technology can do. Thank you.

MEMBER BAILEY: Dr. Koenig.

DR. KOENIG: Good afternoon. I just want to say I'm very honored to be invited to present to this group. I served on a previous

secretary's advisory committee, the SACGT, the committee on genetic testing. And it was interesting to hear that many of the debates are still going on and seem very familiar to me. I appreciate the big task that you have here. I am one of the PIs of the UCSF NSIGHT site, which we called NBSeq or "NuBSeq".

Our project is quite different than the other three. The main goal is to explore the potential application of whole exome sequencing to public health newborn screening. Unlike the clinical case that you just heard -- clinical cases of kids in the NICU -- this is very different.

Specifically, we're trying to evaluate the feasibility of whole exome sequencing to replace or augment tandem mass spec for metabolic disorders. Recall, as Don described to you, the three components that are required in each NSIGHT location, the genomic sequencing clinical research and the ELSI component. I'm going to tell you about our three different components, which involve a collaboration with the California State

Department of Health and the newborn screening programs there. Let me quickly walk you through these three components. Project 1 involves taking 1,570 dried blood spots from the California Department of Health biobank, and then actually doing the sequencing of those specimens. I want to also emphasize, at this point, that I'm not the scientist on this project.

I'm the ELSI person, so I'm going to be fairly general about any of these issues and direct you to my colleagues for any specific questions about the nature of the sequencing technologies, for example. But the bottom line is we're taking all of these blood spots, and then trying to actually do comparisons to look at whether the labs got it right, using that as a gold standard.

Were the true positives actually positive, and were we able to actually detect false negatives, etc.? The project extracts and sequences the DNA, and then annotates a set of 90 primary variants. Then we're working with a group of fabulous computational biologists at Berkeley

and other places. Then we identify the variants associated with the metabolic disorders and do these comparisons to actually see if we're able to call the particular case correctly. I just want to say that all this was done in a double blinded way, and we just have broken the code recently from our first, about 180 samples. I, unfortunately, can't give you results yet because we're just in the process of doing that.

Project 2 will be a bit more familiar, I think, to this group, in that it builds on some previous work on SCID, on severe combined immunodeficiency. What we're actually trying to do in this project is, with a smaller number of consented families, actually taking about 50 families of children who now have presented with immunodeficiency and see if by going back to their newborn blood spot, we would have been able to predict their disease in a positive way, in the way that's now done with the TREC assay.

That's Project 2, much smaller consented. Obviously, our Project 1, with all

those, is purely done with de-identified samples from the biobank. We're very different than the Rady Children's Hospital. Project 3, which is the project that I lead in our group, is really asking the question how will next-generation sequencing enhance, challenge, or transform traditional state-mandated newborn screening, and how should it? We're really trying to get at some of the normative issues, look at some of the legal challenges. I'm not going to -- we have a couple of projects. We're trying to look at incidental findings in the research context and working with our IOB to see how to manage those.

We have a project of determining the views of key stakeholders, such as pregnant women, pediatricians, and obstetricians. We also have a legal project as part of our group. We're looking at the constitutional issues raised by the potential incorporation of whole genome analysis into newborn screening because that's obviously going to be quite a challenge.

Then finally, in collaboration with

other NSIGHT investigators and with the Hastings Center, which is a bioethics think tank, we've convened a national policy board that's going to develop and disseminate recommendations about the appropriate use of whole genome analysis in newborns. Others in this room are part of that group, for which I am greatly appreciative. Most parents don't even remember that they've had newborn screenings. When we went to ask stakeholders, they said things like this: "I don't really remember. My son was a preemie. I had a C-section. There was a lot of crazy stuff going on, so I have no memory." A parent of a child who had immunodeficiencies had a slightly different view: "Had somebody asked me, after all the trauma of giving birth, do I want an additional test on my child, I may have said no, and I would have regretted that decision, so I think everyone should do it because there is no risk."

Those quotes are meant to set up the idea, I think the starting question that we have to ask, or one of the things that I try and ask,

is what is the appropriate balance between parental consent on a one-by-one basis -- relying on consent of parents -- as opposed to public governance, especially of these public health newborn screening programs?

That's the tension. Of course, that tension has been made much more complicated recently by the changes in the law, especially about use of specimens for research. In addition to our NSIGHT project, one of the things we started to discover was this tension, so we wrote another application to NIH, and we're funded by AHRQ, to do a project on deliberative community engagement. I'm going to tell you about that today because I think it's an interesting approach and something that you might not have heard about yet. We created something called a CONSIDER project.

The PI is one of my mentees, Julie Harris-Wai, so I'm presenting for her today. The purpose was to generate informed, deliberative, community-based recommendations to inform critical and time-urgent policy decisions. We

work very closely with the California Department of Public Health. Bob Currier is a great partner in this, but obviously, this presentation -- and this is for Fred -- does not reflect the views of the CDPH.

This is an attempt to conceptualize and visually represent this issue of how much do you rely on consent and individual parental control, on the left side of the screen, as opposed to how much do you rely on governance? For example, one of the activities that you do, as part of this committee, is governance, and community control, and then what should be the balance? I think that deliberative community engagement has a lot of promise in this area. It allows us to move past the limits of individual informed consent. It allows us to actually set up citizens to engage in real trade-offs, set meaningful defaults in the policy arena, consider the impact of false positive results, for example.

You can ask a group of citizens to give you advice on that, rather than just -- since so

few people will face it, and you can address broad public concerns, such as eugenics and privacy versus research benefit. There's a strong argument, I think, in favor -- I'm sorry; I'm having trouble with this -- arguments in favor of governance. Now, one of the things that you're doing in this room, as I said, is governance.

This is a particular kind of democratic process, in which there are public meeting notices that go on for a meeting like this, for a secretary's advisory committee. However, political scientists and theorists have argued that there are also problematics to the way that we do things in this room, in that that policy process can be captured by special interests, and many people argue that reflects a democratic deficit. The deficit is that you don't get voices of just ordinary citizens who are disinterested. Those are the people who will be affected most by public health newborn screenings, so the approach that I'm about to tell you is really meant to find a way of getting those disinterested people's

voices at the table.

Basically, what you do is to try and convene a group of citizens, help them learn as much as possible about the domain that you want them to make decisions about and recommendations on, create the conditions for them to deliberate, and then allow them to make recommendations. In summary, the key conditions that you have to establish for deliberation are time, good information, and an atmosphere of mutual respect.

You don't want to go out and ask citizens for advice, and then ignore it. It has to be a very respectful encounter. I'm going to tell you about one event that we just held in California in March. We selected 33 participants to represent the full diversity of the California population. I'm not going to go into how to do that today. We included simultaneous interpretation as part of it to allow the participation of monolingual Spanish speakers because about half the babies born in California today are Latina. Of course, many are not monolingual speakers, but we

were trying to accommodate that population.

Everybody who was a participant received a briefing book ahead of time, so that they could be as prepared as possible. We made that available in different languages. It could be audio recorded if you were better able to get information through that source. Then once people arrived, we actually allowed them to interact with experts and hear presentations and ask questions.

This, indeed, is Dr. Jennifer Puck, our expert on SCID at UCSF, describing that process and, as well, people from the Department of Public Health. I just have a few pictures to let you in the room of this event, which just happened. After people do have this learning phase, they then spend quite a long time in large group and small group conversations and deliberations. Those take place over four full days in the method we're using, which is over two full weekends, and all of these activities are professionally facilitated. Here's an example of a small group, and here's an example of a small group reporting back to the large

group after they've come to some recommendations. The large group is where the final decision making happens on the last afternoon.

I'm just going to give you -- I can't go through all our recommendations. I'm just going to go through a few to give you a flavor of what these are like. We don't force consensus. We try and arrive at recommendations that have broad support, but also a key issue is to highlight areas of persistent disagreement.

We try to also note all of the ways when people cannot come to agreement because those can be just as useful for policy makers, as you can imagine. Just to give you an example of a recommendation, one that we talked about was on the topic of how to ask for permission, in this case for research use, without damaging the public health goals of the newborn screening program because we were able to respond to this changing policy terrain that we're in. It's interesting that there was broad agreement. The individuals in our deliberative event thought that newborn

screening programs should remain mandatory, and they felt it was important to clearly separate the activities of the newborn screening program from asking permission for the Biobank program, which is obviously complicated to do.

Again, this is an example -- the vote is not the key, but in this case, it was a universal agreement, and in this case, almost everyone agreed with that recommendation. But some issues were more significantly divided. Here's another example of a topic that we deliberated about. The California Department of Public Health should have a policy allowing return of results for biobanking research.

It's the classic return of results question, which I don't need to describe for this group. But in this case, obviously people understood that it was very complicated, so there was considerable disagreement. In this case, you would want to rely much more on consent because there is so much disagreement. Another recommendation that was made, we wanted to ask, at

this point, about what people thought about appropriate use of all the existing biobank samples that exist in the state, which are obviously a source of great tension. The recommendation was samples that were collected without permission, prior to the new 2015 law, first, should not be destroyed, should not require contact and permission to be used, and should be the subject of public education to raise awareness.

I'll give you one or two more. Another recommendation, a very strong recommendation, is that it is appropriate for existing samples to be used for external research, to benefit health and wellness, but probably not for other things. Then finally, we asked a lot about what constitutes trustworthy biobank oversight.

The conclusion was that information that enables full transparency makes the biobank trustworthy. There was a lot of discussion about how particular communities felt that they did not get adequate information, and that was very much a theme among the Spanish speakers in these

deliberations. The last recommendation was that a community advisory board should collaborate with the California Department of Public Health on decisions about how to return results from research to individuals and families. We have several accomplishments of our site. You can look at this later. Essentially, we've sequenced 600 dried blood spots. We've set up this pipeline. We've published several ELSI papers.

We have a special issue of Hastings and a report in process, and we've held this deliberative democracy event. So we think it's been a wonderful experience to be part of this network. My last two slides, for you to look at at your leisure, are all the collaborators. This does take a team of thousands. This is all the NBSeq project funders and collaborators. My final slide, these are all the considered deliberative democracy project collaborators. Thanks very much.

DR. GREEN: Thank you very much. Good afternoon and appreciate the invitation to speak

here. It's been a really diverse group of folks and a really diverse group of approaches. Our approach is very much not a newborn screening approach. Our approach is in sick babies and in well babies who want to be sequenced, whose parents want their babies to be sequenced, what are the outcomes of doing this? This project has all of the institutions you can see here, and we have called it the BabySeq project. It really has to do, again, with voluntary desire for these things, which is, of course, a very different psychology than mandatory issues in this.

We are supported by NIH. You heard the supports for the BabySeq project at NSIGHT. I'm also supported mostly by NHGRI and DoD. These are my disclosures. The program that I lead at Brigham and Women's Hospital and Harvard Medical School we call Genomes to People.

This is a program that tries to investigate the medical, behavioral, and economic impact of sequencing, under a lot of different situations. It may help you to understand what

we've done over the past 15 years, so I'm going to go through it in one slide. We've looked at a single SNP that connotes risk, and we've looked in four different randomized clinical trials at disclosure of this SNP and looked at it from many different angles.

We've looked at direct-to-consumer testing, with the largest number of people responding to how direct-to-consumer testing influences their lives and their health. We have the MedSeq project, which is one of the sites in the CSER consortium, in which we sequence people with a hereditary component, in this case, cardiomyopathy, and we sequence healthy adults in a randomized trial format.

You're going to hear a minute or two about the BabySeq project. We're following people throughout the entire country who are healthy individuals who have elected to be sequenced themselves. It appears that we're going to be under contract for the first pilot program in the active duty military to sequence individuals.

The BabySeq project is essentially two parallel randomized control trials. We are hoping to enroll 240 infants from the NICU at Boston Children's Hospital and 240 healthy newborns from Brigham and Women's Hospital. In each case, they will be randomized to standard of care plus an enhanced family history, or standard of care, an enhanced family history, and whole exome sequencing. Then we follow them with a true plethora of outcomes, economic outcomes, medical outcomes, psychological outcomes in the family, tracking the medical record, and looking at them in many, many different ways. One of the first questions we asked when we were preparing for this grant is do parents even want their healthy babies to be sequenced?

We asked 500 parents, who were actually on the newborn unit immediately after they gave birth, whether they would like this for their babies or not? What was fascinating is that a large proportion of them said they were extremely interested, very interested, or somewhat

interested. If you just took the extremely and very interested, you got about 46 percent of people.

Almost half the people said they were interested. Who wouldn't? You could learn more about your baby. You might find out something that you could treat ahead of time. As you're going to see, the situation looks very different when you are offering them this in the context of randomized clinical trial, where equipoise forces you to provide both the benefits and the potential harms. Really, there's no process for doing this. No one's ever really done this in a systematic way, so we had to make a lot of decisions and would love some feedback from you on these decisions over time. First of all, what categories of results should be reported? Our philosophy, in Genomes to People, has always been try to report everything.

Don't make an artificial distinction between actionability and non-actionability because what's non-actionable today may be actionable tomorrow, and people very often say they

want to learn things, even if there's no treatment. So we came up with, really, two different strategies, one strategy for the well babies, and one strategy for the NICU babies.

For the well babies, we are providing risk for childhood onset disease. That means dominant diseases that have one abnormal variant or recessive conditions, where we've been able to find two abnormal variants for compound heterozygote or homozygote. We're also giving back carrier status for childhood onset disease and some sample pharmacogenomic variants that are at least theoretically relevant to pediatrics. For the NICU babies, we give back all of this, no hesitation. They're all secondary, of course, to the reason that the babies are in the NICU. In this case, they're sort of unanticipated findings for healthy newborns, but they're secondary findings for NICU babies, and there is an indication-based analysis, where genes that are associated with the infant's clinical features are specifically focused on.

To draw a distinction, what you saw in the previous at Rady's was focusing on this. We are focusing on all of this, even for the little sick babies in the NICU. The next question, of course, is how do you give back this information in a way that the caregivers, all of the NICU doctors and nurses, could potentially understand?

There, we were helped by our three or four years of experience in the MedSeq project, where we had generated a low-tech, but we hope highly understandable, one-page summary of whole genome sequencing. In that case, we had a monogenic section, a carrier risk section, a pharmacogenomic risk section, and a blood group antigen section. Then we had a full report coming behind this. The primary care docs that we provided this to in the MedSeq project found this very useful. We actually have all sorts of follow up on their utility of this. But this has framed our production of a report for the BabySeq project, as well. Then we were forced to confront what genes we would like to report on.

Many of you know that our philosophy would naturally lead us to report all genes, including adult onset conditions, but this was not something our IRB decided they were comfortable with, so we did restrict ourselves to childhood onset conditions. We carefully had the molecular scientists in the LMM, under the direction of Heidi Rehm, curate 1,500 genes from various sources, the Bell article, the most likely genes that they're finding in the LMM on children, and of those, put them into these three buckets.

So 818 genes were felt to have childhood onset disease, strong evidence for disease gene association, and relatively high penetrance. Of course, an estimation of penetrance is often a very crude estimation of penetrance, but to the best that they could do, this was the group that we always reported. This group, adult onset, limited evidence, low penetrance, we decided not to report, and this group, we decided to discuss, in each case that we found them, and to make some ad hoc decisions about reporting back. But of course,

once you've got your genes, you've got to decide what categories of variant classification you're going to report back.

In this case, you've heard the five basic categories. We made a clear decision that in our healthy babies, we would report back pathogenic and likely pathogenic, and absolutely not report back variants of uncertain significance or below. Whereas, in our indication-based analyses, principally the NICU babies, for the specific indication, as is consistent with current molecular care, we report back variants of uncertain significance.

Now, what we leave open and nobody's used yet, is in the healthy babies, if they get a condition and they want to come back to us -- let's say that little healthy baby develops a severe atypical asthma. We can now go and do an indication-based analysis around the asthmatic symptoms, and in that case, we will dip into variants of uncertain significance for that indication. You may ask how are we doing with

recruitment? The good news is that we're recruiting, bad news is that -- or perhaps you would say the appropriate news is that people are very hesitant in both categories to sign up for this study.

In the ICU cohort, we've approached 300 families, 41 of which were interested enough to basically hear more, have what we call an enrollment session. Of those, 25 signed consent, and 21 were fully enrolled, of whom we've completed disclosure visits with 12. I think depending on how you see this, this is either a triumph of informed consent or sort of a sad epiphenomenon of the IRB because what we've had to say to people is here are the potential benefits to your baby in the NICU, but here are all these theoretical harms.

These theoretical harms include, for example, discrimination once the baby is an adult. I don't put those things on the same plane, but very often, the family does. You'll see in a moment the reasons for which they're declining. In our healthy babies, we've approached 1,848 families,

and for the same overall enrollment rate of 6 percent, we've had 188 attend the pre-enrollment session, of whom 110 have been fully enrolled. Now, one piece of data I thought you'd be really interested in is why are they saying no? It's important to see the blues before they actually hear more about the study.

We walk in the room and we give a three-sentence introduction, and 50 percent of them say no because of logistics. They're overwhelmed by what's going on. The next highest is they're not interested or uncomfortable with genetic testing, or they're just plain overwhelmed. Once they get through that filter and much fewer sit down and talk to us about the study and hear the pros and cons -- this is very interesting.

Look at the red bars. The two highest reasons are confidentiality and privacy and the potential to receive uncertain or unfavorable results, with fear of insurance discrimination right behind, with 20 percent of people. That's

pretty remarkable. If we could take away the fear of insurance discrimination in some way, we'd get a lot more people who are interested in participating in our clinical research, which I think is an important issue. What have we found among those who have been sequenced so far? We've found, first of all, our time from DNA extraction to report averages 50 days. We can do faster time if it's clinically indicated, but we've had no need for that thus far.

We found that 43 out of 47 infants have at least one recessive allele. This is not surprising. If you look broadly, you're going to find that people are recessive carriers. We hope this is going to be useful to those families, in some cases for planning next reproductive steps, and we're tracking that very carefully.

Two out of the 47 infants had a reportable PGx variant, and three had unanticipated dominant monogenic variants. Here's two out of the three. One was for supravalvular aortic stenosis; one was for dilated

cardiomyopathy. Those babies have been worked up for those and have no signs or symptoms of the condition. Their parents have no signs or symptoms of the condition. We are able to track which parent the variant comes from. We're tracking how much this costs, and how much distress it causes. I think you'll be really interested in the third case because although we were committed to not reporting adult onset conditions, we felt it important to look, in the lab, for adult onset conditions because we thought it was very important to know how many we weren't going to be reporting.

Guess what the very first one was? The very first one that we found in a baby was a BRCA2, well recognized pathogenic variant. When we checked, it was in the mother. Now we had a real ethical issue. Our protocols said we're not returning this to the baby, and yet, how do you feel about knowing that this mother is carrying this and not doing anything about it?

I felt pretty bad about that. We talked at length with our IRB. We have actually

created a deviation from our protocol in which the parents were given the opportunity to learn. If they wanted any adult onset condition, they opted to learn that, at which point we were able to disclose this to the mother, who turned out to be very grateful for the information. There's one other wrinkle to this, which I think is really interesting. Here is the family history of that family. There is absolutely no history of early onset breast cancer. This was not some random family history. This was a three-generation gold standard family history taken by a genetic counselor. But after we disclosed this information, you know what the first thing the mother said was? "Oh, that explains it."

We said, "It explains what?" What that explains is that in fact, there was a whole wing of the family that they hadn't told us about, which had pancreatic cancer, colon and lung cancer, breast cancer, and ovarian cancer. Now, this makes a lot more sense to this family.

For all of us who have said, at some

point in the past, we don't need to apply this in ultimately healthy people because a good family history will pick this up, it just ain't always so. Sometimes, we're going to find things first, through DNA, then circle back and find symptoms, signs, or family history that support them. Like the others, this is a very, very multi-disciplinary project. I'd like to especially acknowledge that we are multiple PIs. I'm a multiple PI with Alan Beggs at Boston Children's Hospital. We have a very wonderful leadership team with Amy McGuire, Heidi Rehm, and the others you can see there. We're very grateful for the support of NIH and all of you in exploring this work. Thank you very much.

MEMBER BAILEY: I invite the four panelists to come and sit on the hot seat. Also want to thank them for sticking with the time schedule. Everybody has a lot more information that they would like to provide. Of course, we tried to limit it to 15 minutes for each center. If you look across these presentations, you can see

there's quite a diversity of kinds of things we're studying, babies we're studying, questions we're asking, but also quite a few commonalities, as well.

Some of the differences that we see across sites may be differences due to measurement differences. It could be due to approach differences. That's the price you pay when you have multiple projects funded -- we're competing going in, and then trying to work together to do some collaborative work and sharing as much as we can across the four groups. With that, I'm going to open it up. I think we have about 20 or 25 minutes for any kind of discussions.

CHAIR BOCCHINI: Joan?

MEMBER SCOTT: Thank you very much, everybody. That was really an insight. I'm trying to absorb because there was a lot of information there. I'm going to ask Robert, because you were last, so that's as far as my memory can take me, but just for point of clarification, the 818 genes that you're giving results back, is

that conditions, or that's genes?

DR. GREEN: That's genes. They're both dominant, recessive, and --

MEMBER SCOTT: But how many conditions does that represent?

DR. GREEN: I don't have that number off the top of my head, but it's slightly less than the number of genes, maybe more like 400-500.

MEMBER SCOTT: Then your slide which you showed the reasons that parents declined to participate, that was from both groups, is that correct?

DR. GREEN: That's correct.

CHAIR BOCCHINI: Cathy?

MEMBER WICKLUND: Thank you for the presentation, you guys. I really enjoyed it. David, this question is for you. When you guys did the sequencing for the NICU patients, did you do a comparative effectiveness? How many would have been detected by standard methods versus -- if you would have taken that baby through the same process standard versus doing the sequencing, how many

would have gotten to the same place?

DR. DIMMOCK: Yes, is the short answer. The initial study at Kansas City was set up as a randomized control trial, randomizing patients to either get standard of care or rapid genome.

In that study -- and almost the same data was actually generated from a similar parallel study that's not yet published -- the background diagnostic rate, actually across groups, would have been 7 percent, compared with 57 percent. It's extremely highly statistically significant. So yes, the effectiveness is much higher for the rapid genome than it is for standard of care.

MEMBER BROSCO: Can I ask a follow up on that? I remember when the same data presented was at the SD meeting. There was actually a lot of discussion about how hard it was to enroll in the control group. There was also a lot of debate about what counted as an actionable item, so it wasn't quite as clear as that.

DR. DIMMOCK: Yes, so the 7 percent versus 57 percent is comparing diagnostic rate,

which is a lab measure, rather than a clinical utility measure. The rate of accrual in Kansas City was actually quite low. It was an ongoing problem. As I said, we've been going live in San Diego now for just under a month, and we've put 26 genomes through.

I think the big difference is what the standard of care is now. Offering exome versus genome versus genome versus no genome wide sequencing actually is quite different. In terms of clinical utility, it's a much more difficult place to get your head around. One can argue that by going the palliative care route, you're saving money. I don't think anyone in this room likes the idea of that as a number. When you look at the cost of testing, the back-of-the-envelope calculations, if rapid genome sequencing costs $20,000 for a round of treatment-- which it doesn't, but it's a nice round number -- and it costs $1 million for a kid with significant intellectual disability -- which it doesn't, it costs a lot more than that -- you need to diagnose

about 1 in 215 cases for it to be cost effective.

MEMBER WICKLUND: I just had one more question. When you looked at the final list of potential diagnoses, how did that one jump out? You said that's a large number of diagnoses to try to go through, and then we kind of jumped to this one was the one. How did that jump happen?

DR. DIMMOCK: With some genomes, when you're analyzing them or you're looking at them, you have an a-ha moment. It's very easy. The best example I give is I was looking at, actually, an exome that we got. The indication for testing was tufting enteropathy. At that point, there was one known gene for tufting enteropathy, and the kid was homozygous for a 22 base pair deletion. It's kind of a very easy place to go. The approach that we have right now with the phenotype driven is that we look for an overlap between the diseases that have the HPO terms -- we're using Human Phenotype Ontology, which is sort of a standardized catalog of terms -- that then overlap with variants in genes. We take an overlapping intersection.

When we generate a gene list using this approach, the Kansas City experience is that about 43 percent of the diagnoses are made in that overlap or intersection, and about 60 percent of the diagnoses are made in genes that are not in that overlap or intersection. So those are hand review of other variants, rather than the semi-automated process that is in the overlap space.

DR. KOENIG: I just have a quick follow-up question, if I could, to that. In the patient with liver disease that you presented, it's unclear to me, thinking back to my clinical days, as to how -- might that disease not have resolved on its own? That was a little piece that I missed.

DR. DIMMOCK: I don't have the benefit of having taken care of this child clinically, but HLH is a very difficult diagnosis to make, and many of the children end up with really severe end organ damage before a clear diagnosis is made. I think my expectation would be that this child would have ended up in end organ failure if they hadn't had some form of prompt molecular diagnosis because

it's clinically a very difficult diagnosis to make in a newborn.

MEMBER PARISI: Melissa Parisi, NIH. Thank you all for some excellent presentations. Obviously, we've been very excited to follow these projects as they've evolved. I had a question for Robert and David about the logistic challenges of enrollment and recruitment. You showed a slide, Robert, where that was the overwhelming pre-counseling session barrier.

I don't know whether that was different in the NICU families versus the healthy infants, and if there are any strategies that you have taken, or also from your experience in San Diego and Kansas City, to help facilitate education and recruitment, given the challenges that sometimes are placed before us, with regard to dealing with IRB requirements of informed consent.

DR. DIMMOCK: We were talking about this over lunch, so I can go first. I am actually going to pull on some of my Wisconsin experience, as well, because I think it is pertinent to this.

We offered clinical rapid sequencing in Wisconsin. I think I can think of one occasion where we had somebody decline testing, of hundreds.

The experience in Kansas City was the exact reverse, where they were going days or weeks without getting a single case enrolled. At Rady, we're kind of somewhere in between. I think the concept of consent is an interesting concept in an ICU with a parent with a critically ill child.

I don't think any consent is really valid in the ICU, but we can argue that over beers some other time. Really, in this situation, most families will look to their ICU doctors really as kind of a proxy decision maker. So the opinion of the ICU doctors has a huge influence on whether or not parents choose to do testing. The opinion of the ICU doctors largely depends on their experience. When we were in the situation with Wisconsin, where we'd had a series of life-saving successes, it was very easy to enroll patients for clinical testing. Among some of our minority populations -- we presented this data before in

Wisconsin -- when we were requiring research consent, they would decline because they didn't want their babies experimented on.

When you offer something as a cutting edge new test, it's quite exciting. So I think there is this huge hurdle, when we require written IRB consent, that actually really affects any meaningful idea of what real uptake will be when you remove that artificial hurdle.

DR. GREEN: I would agree with that and just add that framing seems so important here. Even if it's a research study -- Geisinger's getting very high proportion of people saying yes.

Inova, under some similar circumstances to ours, is a very high proportion of people saying yes. I'm not saying that they're not telling the truth -- I think they are -- but how you frame this is really important. Putting it in a randomized clinical trial really emphasizes equipoise because you're saying -- you can't even say to the person, "It's research, but I think it's going to help you." You're actually saying, "I'm

going to randomize you into an arm that doesn't have this and an arm that does because we don't know if it helps you or harms you."

That really drives home the point. I'm proud of that because I think our data's going to be really rigorous, but it's really hurt our recruitment, that and the framing that the IRB insisted upon. In some cases, we disagreed significantly with what they said, and we've made some adjustments, but we are of different minds about some of the future danger.

DR. DIMMOCK: I wanted to just kind of finish up that thought. There's two other studies that I've been involved in that are NIH funded, where we've had very interesting issues. One study involves taking a family health history on a computer-based tour, rather than in person. We've had about a 1 percent uptake for that study of taking family history. I don't think you can argue that this is particular to a study that involves genome sequencing. This uptake of research is a systematic and systemic problem.

Similarly, we've had an issue where another study that we're doing, we're offering standard of care testing as a result of finding mutations in hypercholesterolemia genes.

The IRB is requiring us to get research consent on the family members to do standard of care cascade screening. We're having a real problem with actually being able to get people tested through the protocol, but they'll pay the money to get tested outside of the protocol.

MEMBER BAILEY: If I could just add to this. Obviously, one of the titles of one of the articles that I showed you was do parents really want this? I think we can't just -- it's not an easy answer because the context in which we ask them, as you've heard already, drives so much of the decision, whether they have a sick baby or not, whether it's been presented by a researcher or a clinician, or a host of other reasons. As you know, Dr. Parisi, in our project, we're going what we like to think of as going beyond informed consent to informed decision making. Based on the

literature on patient decision making and informed decision making aids, we developed a tablet-based tool to help parents go through the process of deciding, not only just presenting here are the bad things that could happen, here are the good things that could happen, but in helping families understand that and how it might map against their personal values and preferences.

It will be real interesting to see how our uptake rate occurs with regard to that. It would be really unfair for us to say we had a better uptake rate than them because of that because everything else is different about the project.

So there's need to be much more study about this, but I think there have been so many surveys of families. The history of this is you can ask parents their feelings a lot, but when you then actually offer something, it changes the dynamic considerably. That's why you have to do studies where you actually offer things.

MEMBER BAKER: This is Mei Baker, question for David, quick technical question. I

was wondering, when you talk about this diagnosis rate, 57 percent, is the sequencing alone, or you have array, also?

DR. DIMMOCK: The 57 percent diagnosis rate is based on the genome-wide sequencing. Our ability, in the rapid protocol, to call structural variants is limited. We do have the ability to replace micro-array with genome sequencing, but that is not part of the current clinical report workflow. That 57 percent actually doesn't include chromosomal abnormalities. It's actually a problem right now because we have genome results a week or two before we get a micro-array result back.

MEMBER TARINI: Beth Tarini. I want to put a plug in for the ELSI program, since it seems that despite presenting much data anchored in the genetic science of it, most of this discussion is focusing around the actual ELSI implications of doing the work in both the clinical setting, as well as the research setting. I think that's interesting. I was curious what the panelists

think, what do we do with this poor uptake in research issues? Do we toss informed consent? Do you think we should change it? Do you think we should circumvent it by claiming some of these are clinical issues, really, and to say that they're research is problematic, from a larger ethical perspective, because it prevents us from actually getting useful data and/or helping people? I just was wondering what the thoughts of the panelists are?

DR. POWELL: I think that if we could educate everybody way ahead of time about, whether it's newborn screening or genetics, genomics, that would really be ideal because faced with having a baby in an intensive care nursery is not a good time to try to explain to people about what are genes and what's sequencing and what might this tell. I think the other thing is on the social policy end of things. If people are concerned about their insurance and future problems, we really need to address that from a much bigger policy area.

DR. KOENIG: I think I would just like

to add that I think the bigger problem is that in the whole human research protection arena, we ask informed consent to do way too much work. We ask it to do way more work than it can possibly do. That's one of the reasons that I'm so interested in moving toward thinking about other approaches that can help people think collectively about some of these issues, and maybe set policies and practices that rely less on whether you can actually get a signature at that particular moment in time, which may be somewhat arbitrary.

I think it's a particular issue when we're trying to talk about -- we're now being challenged by these technologies and by big data projects, in general, and by all of the fact that we're going to have to follow so many people over so long to get answers about most of these questions that are now on the table.

The traditional method of calling something research, hiding it off, and then having this set of requirements associated with it is really not working anymore because the boundary

between what's research and what's clinical or what's public health practice is just dissolving as we speak. We're at a very challenging moment.

MEMBER BAILEY: I think from these projects -- these were exploratory projects in many ways, even though they are research. I think ultimately, from these, we'll have a much clearer sense of -- it won't come at the end of these by saying, "Here's the answer to your question," but I think hopefully we'll be moving it down the road and maybe being able then to do more systematic cross-site studies answering those questions in more definitive ways.

CHAIR BOCCHINI: David, did you want to add?

DR. DIMMOCK: I did. As I said, I don't think that consent is meaningful in the ICU. I really don't. I think what I see us often.

MEMBER TARINI: Research or clinical?

DR. DIMMOCK: Yes. We have to make sure that the physicians that are interacting with the families really know the limits of what we're

proposing to do. We need to move to a point where it's equipoised to do the research or not, which, in most NICUs in the U.S., means bringing up the standard of genetic testing at least into the 1980s.

I think the other challenges we see is the issues of requiring written consent. Most IRBs require a form to be translated into the patient's language before they can sign it, before they can enroll. In a population as diverse as San Diego, or even Milwaukee, we don't have 40 or 50 translated consent forms available. So I think the whole concept of what is consent and what is getting something written are two very different things. I really appreciate the concept from the UCSF group in actually really getting a community input into what we should be doing, so that it's not dependent on the whims of a physician and how sleep-deprived the parents are that day.

DR. GREENE: Carol Green, SIMD. I have a question, but also a couple of observations. The question has to do with the 1 in 50. I've

always been troubled by that, and it is standard, but the carrier frequency for PKU is 1 in 50.

So I've always been troubled by excluding things by only looking at things unless they're less -- or 1 in 100. They have to be less common than 1 in 100, or you ignore it. PKU carrier frequency is 1 in 50. That is the question. Observation, on a very, very, very, very, very, very limited scale, we did something comparable to what Kansas was doing. We were in communication with Kansas. We had either 3 for 3 or 4 for 4 accepting, but we were not asking people right at the moment of delivery and the beginnings of the chaos, but we were picking babies who were diagnostic dilemmas. The family was already invested in and interested in truncating the diagnostic dilemma. That's one way to look at babies.

We did not have such a diagnostic rate, so always wonder about are we really finding the explanation of the whole disease or some little part of it? One of the ways to get the consent on

the control babies will be to ask before the baby's born, when you're not in the middle of all that chaos. I'm not so terribly worried about the consent. I also did look it up.

This is 2006 Review of Fetal and Neonatal Histiocytosis. I can't get the whole article, so there may be all sorts of different kinds. This study, they reviewed 221 fetuses and neonates. The study suggests there is an increased incidence of spontaneous regression of histiocytic lesions in neonates, as compared to older individuals. My question is about the 1 in 100.

DR. DIMMOCK: That's an easy one to answer. There are actually six diseases, or actually six variants that are neonatal or early childhood onset that cause disease that have a population frequency above a half percent. Yes, we're well aware of them, and actually, our computer algorithms specifically pick those out.

PKU actually isn't one of those because there are several frequent variants that combine

to count for the 1 in 50, rather than a single variant. So yes, it's a problem. If you set a cut too high and you don't have the algorithms to allow for those six variants, then you're going to miss them.

(Off microphone comment.)

DR. OSTRANDER: Bob Ostrander, American Academy of Family Physicians. It's interesting. We're primarily focused here on the social dynamic of this and not on the science. I find when I'm teaching about quality improvement, no one wants to be there, but they have to be, until I remind them that the thing that's getting in the way of their practicing medicine isn't their lack of knowledge; it's these process issues. I think this applies here. It strikes me that we're trying to do 21st century research with mid-20th century ethics and IRB processes that were really designed around the specific issue of randomized control, prospective style trial of treatments of things that you didn't know were worthwhile. I think it's great that your studies are exploring that and are

going to publish on that, but I think we really need to do some translational publication and research with current ethics to pull this together.

That's the 30,000-foot view to what your day-to-day issues are. I find that this culture, compared to other cultures, as I read other literature in my day-to-day experience, is very risk averse. So if you say there's a risk of something, you're going to get a no, and because you have to reach equipoise, you have to give them the risk.

I have found it helpful -- again, I don't know if you guys have tried this. This is where the question is embedded. Have you tried to quantify the risk for them? When you look at your bar graphs, the things that they were most afraid of were breaches of privacy and insurance company discrimination. The bad news is a real risk. What's the quantifiable risk of breach of privacy? There's so much media, and the legislative people are so focused on this stuff, as if there's an immediate danger to everyone. The quantifiable

risk, I think, is very, very, very, very low. If you can put it in terms to folks, that may blunt some of this.

Yes, this is the risk, but it's less than the risk of you getting hit by lightning on your drive here to get your kid tested. It's 1 in 100,000, the same as we talk about blood transfusions. Likewise, when you're talking about the insurance denials, maybe life insurance, but under the ACA, nobody can be declined health insurance because of this. You could dispel a good chunk of the nos by stating the risk, but giving it a number. I think being quantitative with patients helps at least a fairly large subset of them.

DR. GREEN: Yes, that's an excellent idea. I don't think we've done that, and we should try it. I know that at some point, we tried to inject some language about the insurance discrimination, but there's been no specific case of life insurance, and that was rejected, in part because we're actually warning them of what could

happen once this child gets to the age of 18 and nobody has any idea what the circumstances are going to be at that point. But I'll go back and try that some more. I think that's a really good idea. It also could be quantified on the positive side, too. If you now have data that in a NICU, among people who agree to it, you've got some high assistance with diagnosis rates, that's right, you could put that in. That would be helpful. Thanks.

MEMBER BROSCO: So a couple of comments. One is, again, remembering David, when the information was presented at PAS about Kansas City, I think it's important to separate out consent for research and consent for genome sequencing.

Because it sounded like the Kansas City experience was a lot of -- the clinician said, "We want sequencing. We're going to do it on this kid," and it wasn't so much that the families didn't want it; they didn't want it to be randomized to control. I don't know if that's true, but that's

what I remember being reported. So we should separate that out. But again, I want to come back to this idea that the controls are actually really important. Because absent that control group, it's hard to know what the added benefit of genome sequencing really is. That's critical. There are models out there. I love Barbara's approach.

We know, for example, in field research on resuscitations, where informed consent is impossible, you can do community-based kinds of consent. I think this is worth doing because this is a huge question for all of us. If we don't answer it well now, we're going to be stuck with everyone wants the sequencing done, and we don't know if it really helps.

DR. GREEN: Not only that, but there are companies that are using research standards to circumvent clinical care. They are saying, "Come get this product," and that's the message. "This product will do X, Y, and Z." Then they're actually having their participants sign a research protocol. In some cases, they're

charging -- there's one company charging $25,000. So you pay me $25,000. I'll give you a research consent form, and I'll sequence you and talk to you a whole lot about other cutting-edge technologies. That implies a certain value. There's a transaction going on there. There is a consent. It's IRB approved. It's a commercial IRB. But the danger here is that workarounds like that generate all of the evidence that's out there because the processes get in the way of us trying to generate evidence. That would not be a good outcome, either.

DR. DIMMOCK: I would agree. Our biggest fear is that we actually don't get the evidence before it becomes standard of care. We were there with micro-arrays. I think we're almost there with exomes in certain specific situations now, where it would be considered unethical to randomize people to no testing because insurance covers an exome.

This was a problem we were aware of six years ago, and we couldn't get randomized trials

funded then. We're now at a point where we can get the trials funded, but the standard of care has changed such that it's very hard to prove. I agree with you. We need to move this beyond just does the test work, but does it change care, and does it make a difference.

MEMBER SAARINEN: Hi, Annamarie Saarinen. Thank you so much for all of your presentations. Bear with me, since this is my first time speaking in front of this whole committee, so thanks for letting me weigh in at the end here. Robert, I'm sorry I didn't recognize you earlier from our dinner last fall in Boston. It's good to see you and hear more about your work.

You touched on a little bit of what I was going to comment on. What you're getting from the NICU population seems like it could, in very real terms, be used in a way to support the control group and information that can be provided to families of well babies. I agree with another point about -- again, before birth, not in the I just had a baby setting, and here's a bunch of

information that's being thrown at you.

We had a conversation last night about approaching parents about things like trials when they're under duress. I've been under duress a lot with my kid, both my children. The NICU is a place of duress, so it's very difficult in that setting. But the clinical advice that's being given, as you suggest, is really what's driving the next level decision. If what we're getting to is a place where this could become a population health thing, then at that point, how does what's going on in the well-child nursery impact what is happening in a setting where a child is already unwell, potentially, in terms of ordering that test or moving forward?

Then my futuristic question is if all of this were affordable and feasible today, based on the knowledge you all have now, do you think population health full sequencing of newborn is a good idea?

DR. KOENIG: Could I just respond really quickly about one thing that I think I wasn't

clear about in our research, partly because I'm the ELSI researcher? The big purpose of the UCSF project is to ask two questions, which are directly relevant to the work of this committee.

One is the issue of would the sequencing, as a technology -- is it actually good enough to do the work that's now done by other methods? Does it actually work, if you compare it to what the current gold standards are? Then the second question is regardless of how you answer that question, might it also have utility as a secondary test, when you have a confusing or a result that you need to follow up? I just wanted to make that clear. Those are really, I think, the important questions that we don't know the answers to yet. I just want to highlight that in response to your comment.

DR. DIMMOCK: I'm happy going first with the question that nobody wants to answer. The cost of testing a child is not just the cost of doing the sequencing. The cost of analyzing the data is probably twice to three times the cost of doing the

sequencing would be a conservative estimate right now because it's not automated.

Beyond that, you have the cost of downstream testing to confirm or refute a diagnosis, and then you have the downstream costs of theoretical harm. I'm going to agree with Robert on this that I think it's theoretical. The data from some other diseases would suggest actually knowing your child has a diagnosis does more benefit than harm, and growing up knowing you have a risk of something like breast cancer, actually, you have a better psychological adjustment. I think we have to consider all of those costs in totality. We have to consider all of the benefits in totality. One of the public comments earlier on was about GAMT deficiency. There are over 60 treatable causes of intellectual disability. My worst place, as a clinician, is being in a situation where we diagnose something that would have been treatable if we'd known earlier.

One of the recurring themes around this

table, though, is is there enough evidence of doing that testing to risk subjecting families to harm or misdiagnosis, which may lead to an intervention that hurts more children than it benefits? I think we have to walk in a case-by-case scenario.

In the intensive care units, the evidence is getting there that it actually improves care. I think we probably have a couple more years, at least, before we can say it is the area of intellectual disability which affects, if you extend the area to NDD, about 3 percent of the pediatric population, that's a huge area. We know a subset of children with diagnosis of things like autism have treatable disorders. The challenge we have is we need to get there and do the trials before standard of care becomes genome, to work out whether or not it's actually worth doing, not because I don't want to test people, but I don't want to hurt people by giving wrong diagnosis or treatment that is ineffective or wrong. I think then, when we get to a point where we're comfortable with knowing what diseases and what normal is, we

can then think about offering it into a wider, well population with appropriate consent.

DR. POWELL: I'm not at the point to start arguing that given no financial limitations, we should start doing this on a population-wide basis. I do think we need to start thinking about groups of conditions that we otherwise aren't going to be able to detect any other way, that we could pick up through molecular analysis, whether it's genome or exome sequencing.

I think that we just don't know enough yet about the penetrants of these conditions. As David was saying, what's the chance of someone with what we think is a deleterious mutation developing the disease? We know that there's 100-year-old people who have what we think are pathogenic mutations, who have never gotten sick from that condition. But then again, what about the benefits that you could bring by detecting kids who will go on and have the condition? We do that now with MCAD, sort of the poster child for the use of tandem mass spec and previously expanded newborn

screening.

We know that a third of those patients will never develop problems, a third will die from their initial episode, and a third will have an episode and become permanently intellectually disabled from that. Yet, I don't think anyone would argue against the benefits of detecting that early in a child, where you can intervene.

There's also conditions that we have a secondary test. If you pick up a child with what looks like to be a long QT condition, you could do an EKG to give you more information about that, so there's other examples of that, where you wouldn't necessarily implant a pacemaker or defibrillator immediately just based on that gene information that you get.

DR. GREEN: I agree with both of those. I'll only add that last point, I think, is critically important. Instead of thinking about a genetic result as a diagnosis, think about it as a risk factor to be integrated into history, physical examination, and other laboratory

studies. Suddenly, the equation changes. You're not talking about it as a diagnostic test. You're talking about it as a risk factor to be incrementally integrated into additional information.

MEMBER SAARINEN: Yes, I agree with that. I see that happen with a lot of what we work on in newborn screening, actually, particularly with CCHD screening. But as you were all talking, I thought a lot about -- this may be a horrible analogy, but in my head, I kept thinking about back in the day, when sonography, just having an ultrasound during your pregnancy was like well, we could do that, but we don't have to do that.

I have a 21 year old and a 7 year old, so the difference between that pregnancy and my 7 year old and having an ultrasound, I think I had, what, six or seven of them during my pregnancy then, and how that became oh, we just do that. We find things that we don't always know, that require further testing. It seems a few early-on--

DR. GREEN: To your other question, I

think that when sequencing becomes cheap enough and interpretation becomes a more automated pipeline and people are more familiar with the uncertainties, I think sequencing is going to be exactly like ultrasound. It's not going to be required, but it's going to be routine.

MEMBER TARINI: I just want to point out, except you're both operating with different historical reference points. At the time in which ultrasonography of women was not routine, it is not at the standard it was today. At the time, in a few years, the knowledge and predictability of what you get off a genetic test will be different.

So you can't use -- you have to use different anchor points when you're referencing the medical technology and when it was used and now versus before. You will get to a point, I agree with you, in genetics will be like ultrasound is today. You are probably closer to the beginning, although further ahead than the original ultrasound, which looked not much different than a TV with antennas that went awry. I just wanted

to --

(Simultaneous speaking.)

DR. KOENIG: If I could just add, though, do we want to use that as an analogy, the imaging, especially, given what we know about the overuse of imaging?

MEMBER TARINI: How so?

DR. KOENIG: Just across so many fields in healthcare, yes, do -- this is a slightly different point than what you're making.

MEMBER TARINI: You don't have to convince me that there's a potential for technology, when not fully understood, to be overused. My point is that -- this goes back to what Jeff said earlier, I think, from a historical standpoint, which is we can't look at ultrasound now and say we waited too long because it's so good, when it wasn't at that standard before, much like we cannot say how good genetic testing will be and use that as a reference point for now. We must live in the now and what the limitations of the testing are, as well as the overdiagnosis is one of them.

DR. KOENIG: Right. There is a huge rhetoric now that exists about the importance -- the idea that it would be a fundamental good to sequence every person at birth, but we don't -- that's basically -- that's a rhetorical statement. I don't think that's going to proceed based on evidence. I think it's another social phenomenon that we have to take account of.

MEMBER TARINI: Sure.

DR. GREENE: Carol Greene, SIMD. One thing that has been mentioned and came up in the discussion of adrenoleukodystrophy, totally separate issue, was mentioned already by one person today. Long QT is the perfect example. You can die of long QT with a normal EKG, so the normal EKG on the baby is not necessarily -- but you could find the father who doesn't know that he's at risk for sudden death, who actually gets a pacemaker, and then you've saved some quality lives for the dad. This is going to change the paradigm and the context, as well. It's been brought up, but I just wanted to put it in the middle.

DR. KOENIG: I just want to comment. We were just commenting that everything seems to go back to the debate about the ACMG incidental findings recommendation, which is interesting. I want to just add one other thing, Don. The other thing that hasn't come up in this discussion is that all four of these projects were very much affected by a change in policy of the FDA, in terms of how they would step in or not to oversee some of these projects that use next-generation sequencing in these quasi-clinical, quasi-research contexts.

A lot of us behind schedule partly because of that, too, because we had a lot of interactions with the FDA. One of the big ones was about this issue of impact that might be of potential clinical value outside of just the child, but in the parents, as well. That's not a problem that's going to be easily solved.

MEMBER BAILEY: I think we're probably about out of time, but I wanted to thank you for letting us come and share where we are, which is kind of -- we're in the middle of this right now.

We did propose very clear studies in our proposals, but they've evolved into very much living laboratory kinds of things. We're learning quite a bit from them, sometimes things that we didn't think we -- a lot of it is things we didn't think we would learn when we first started out, so we appreciate the opportunity to share this mid-point, where we are. Hopefully, in another two or three years, we can come back and say more definitively what we've learned.

CHAIR BOCCHINI: Thank you, Don. I want to thank all the panelists. This has been -- you're doing exciting work. This has been a really excellent presentation, so we really look forward to hearing more from you as this evolves. Thank you very much. We appreciate it. With that, we are now moving to the workgroup meetings. Debie, you want to tell everybody which workgroup goes where?

MS. SARKAR: The education and training workgroup will be meeting here, in this room. I think you'll reconvene at 3:10. The

follow up and treatment workgroup and the laboratory procedures standards workgroup will be meeting across the street, at 5600 Fishers Lane. You'll have to go through security, and then we have HRSA staff waiting there to escort you to your room. Follow up and treatment, just so you know, it's in 5 West 07, laboratory and standards is in 5 North 54.

CHAIR BOCCHINI: Before we close, if the four new committee members would come over here, we can talk about which workgroup, if you haven't decided already. With that, we'll conclude today's session. Take a little break before we start the workgroups, and then we'll meet promptly tomorrow morning at 9:00. Thank you all very much.

(Whereupon, the above-entitled meeting was concluded at 3:02 p.m.)