Health Resources and Services Administration

Advisory Committee on Heritable Disorders in Newborns and Children

Meeting

10:00 a.m. to 3:15 p.m.

Thursday, August 1, 2019

Reported by: Gary Euell

P R E S E N T

ADVISORY COMMITTEE MEMBERS

Cynthia M. Powell, M.D. (Chairperson)
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
Pediatric Genetics and Metabolism
The University of North Carolina at Chapel Hill

Mei Baker, M.D.
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health
Co-Director, Newborn Screening Laboratory
Wisconsin State Laboratory of Hygiene

Susan A. Berry, M.D.
Professor and Director
Division of Genetics and Metabolism
Departments of Pediatrics and Genetics, Cell Biology & Development
University of Minnesota

Jeffrey P. Brosco, M.D., Ph.D.
Professor of Clinical Pediatrics
University of Miami School of Medicine
Department of Pediatrics
Deputy Secretary, Children's Medical Services
Florida State Department of Health

Kyle Brothers, M.D., Ph.D.
Endowed Chair of Pediatric Clinical and Translational Research
Associate Professor of Pediatrics
University of Louisville School of Medicine

Jane M. DeLuca, Ph.D., R.N.
Associate Professor
Clemson University School of Nursing

Annamarie Saarinen
Co-founder, CEO
Newborn Foundation

Scott M. Shone, Ph.D., HCLD(ABB)

Senior Research Public Health Analyst
Center for Newborn Screening, Ethics, and Disability Studies
RTI International

Beth Tarini, M.D., M.S., FAAP
Associate Director, Center for Translational Science
Children's National Health System

EX-OFFICIO MEMBERS
Centers for Disease Control & Prevention
Carla Cuthbert, Ph.D.
Chief, Newborn Screening and Molecular Biology Branch
Division of Laboratory Sciences
National Center for Environmental Health

Food and Drug Administration
Kellie B. Kelm, Ph.D.
Deputy Director
Division of Chemistry and Toxicology Devices

Office of In Vitro Diagnostics and Radiological Health

Health Resources & Services Administration
Michael Warren, M.D., M.P.H., FAAP
Associate Administrator,
Maternal and Child Health Bureau

National Institutes of Health
Melissa Parisi, M.D., Ph.D.
Chief
Intellectual and Developmental Disabilities Branch
Eunice Kennedy Shriver National Institute of Child Health and Human Development

DESIGNATED FEDERAL OFFICIAL
Catharine Riley, Ph.D., M.P.H.
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

ORGANIZATIONAL REPRESNTATIVES

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

American Academy of Pediatrics
Debra Freedenberg, M.D., Ph.D.
Medical Director, Newborn Screening and Genetics
Community Health Improvement
Texas Department of State Health Services

American College of Medical Genetics
Michael S. Watson, Ph.D., FACMG
Executive Director

Association of Maternal & Child Health Programs
Jed L. Miller, M.D., M.P.H.
Director, Office for Genetics and People with Special Health Care Needs
Maryland Department of Health
Prevention & Health Promotion Administration

Association of Public Health Laboratories
Susan M. Tanksley, Ph.D.
Manager, Laboratory Operations Unit Texas Department of State Health Services

Child Neurology Society
Jennifer M. Kwon, M.D., Ph.D., FAAN
Director, Pediatric Neuromuscular Program
American Family Children's Hospital
Professor of Child Neurology, University of Wisconsin School of Medicine & Public Health

Department of Defense
Theresa Hart
Senior Nurse Consultant, Defense Health Agency

Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development

March of Dimes
Siobhan Dolan, M.D., M.P.H.

Professor and Vice Chair for Research Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine and Montefiore Medical Center

National Society of Genetic Counselors
Amy Gaviglio
Genetic Counselor/Follow-Up Coordinator
Minnesota Department of Health

Society for Inherited Metabolic Disorders
Georgianne Arnold, M.D.
Clinical Research Director
Division of Medical Genetics
UPMC Children's Hospital of Pittsburgh

PRESENTERS
Scott Grosse, Ph.D.
Economist
Centers for Disease Control & Prevention

Alex R. Kemper, M.D., M.P.H, M.S.

Lead, Evidence-Based Reviews
Division Chief, Primary Care Pediatrics
Nationwide Children's Hospital
Professor of Pediatrics, The Ohio State University
College of Medicine

Jelili Ojodu, M.P.H.
Director
Newborn Screening and Genetics
Association of Public Health Laboratories

Anne R. Pariser, M.D.
Director, Office of Rare Diseases Research
National Center for Advancing Translational
Sciences, National Institutes of Health

Lisa A. Prosser, Ph.D., M.S.
Professor
University of Michigan

Ashleigh Ragsdale, M.P.H.
Newborn Screening Epidemiologist

Office of Newborn Screening

Washington State Department of Health

C O N T E N T S

P R O C E D I N G S

DR. CYNTHIA POWELL: If everybody could take their seats, please. Welcome everyone to the third meeting of the Advisory Committee on Heritable Disorders in Newborns and Children for 2019. I'm Cynthia Powell. I'm the new Chair of the Committee, and it's my honor to take over as Chair. We will begin this meeting by the taking roll call of attendance, first with Committee members. Mei Baker.

DR. MEI BAKER: Here.

DR. CYNTHIA POWELL: Susan Berry.

DR. SUSAN BERRY: Here.

DR. CYNTHIA POWELL: Jeff Brosco is unavailable. Kyle Brothers.

DR. KYLE BROTHERS: Here.

DR. CYNTHIA POWELL: Jane DeLuca.

DR. JANE DELUCA: Here.

DR. CYNTHIA POWELL: Carla Cuthbert.

DR. CARLA CUTHBERT: Here.

DR. CYNTHIA POWELL: Kellie Kelm.

DR. KELLIE KELM: Here.

DR. CYNTHIA POWELL: Michael Warren.

DR. MICHAEL WARREN: Here.

DR. CYNTHIA POWELL: I'm here. Melissa Parissi. Annamarie Saarinen.

MS. ANNAMARIE SAARINEN: Here.

DR. CYNTHIA POWELL: Scott Shone.

DR. SCOTT SHONE: Here.

DR. CYNTHIA POWELL: Beth Tarini.

DR. BETH TARINI: Here.

DR. CYNTHIA POWELL: And Catharine Riley.

DR. CATHARINE RILEY: Here.

DR. CYNTHIA POWELL: And now we'll have the organizational representatives from the American Academy of Family Physicians, Robert Ostrander.

DR. ROBERT OSTRANDER: Here.

DR. CYNTHIA POWELL: American Academy of Pediatrics, Debra Freedenberg.

DR. DEBRA FREEDENBERG: Here.

DR. CYNTHIA POWELL: American College of

Medical Genetics, Michael Watson.

DR. MICHAEL WATSON: Here.

DR. CYNTHIA POWELL: American College of Obstetricians and Gynecologists, Steven Ralston. Association of Maternal and Child Health Programs, Jed Miller.

DR. JED MILLER: Here.

DR. CYNTHIA POWELL: Association of Public Health Laboratories, Susan Tanksley.

MS. SUSAN TANKSKLEY: Here.

DR. CYNTHIA POWELL: Association of State and Territorial Health Officials, Chris Kus. Association of Women's Health, Obstetric, and Neonatal Nurses, Jacqueline Rychnovsky. She may not be able to attend. I don't know if you're on. Child Neurology Society, Jennifer Kwon.

DR. JENNIFER KWON: Here.

DR. CYNTHIA POWELL: Department of Defense, Theresa Hart, who is an alternate for Jacob Hogue. Genetic Alliance, Natasha Bonhomme.

MS. NATASHA BONHOMME: Here.

DR. CYNTHIA POWELL: March of Dimes, Siobhan Dolan.

DR. SIOBHAN DOLAN: Here.

DR. CYNTHIA POWELL: National Society of Genetic Counselors, Amy Gaviglio.

MS. AMY GAVIGLIO: Here.

DR. CYNTHIA POWELL: Society of Inherited Metabolic Disorders, Georgianne Arnold.

DR. GEORGIANNE ARNOLD: Here.

DR. CYNTHIA POWELL: Okay. Next, everyone on the Committee has received copies of the April minutes. Those changes have been incorporated. There was one change that came in after the final draft was sent around, and that has been incorporated -- will be incorporated into the minutes, but that's not on the final draft. That was on page 14. And are there any further additions or corrections to those minutes? Okay. If not, could I have a motion to approve the minutes?

DR. SUSAN BERRY: So moved. This is Sue

Berry.

DR. CYNTHIA POWELL: A second?

DR. BETH TARINI: Beth Tarini, second.

DR. CYNTHIA POWELL: And then, we'll go through a vote to approve the minutes. Mei Baker.

DR. MEI BAKER: Approve.

DR. CYNTHIA POWELL: Susan Berry.

DR. SUSAN BERRY: Approve.

DR. CYNTHIA POWELL: Jeff Brosco is absent. Kyle Brothers.

DR. KYLE BROTHERS: Approve.

DR. CYNTHIA POWELL: Jane DeLuca.

DR. JANE DELUCA: Approved.

DR. CYNTHIA POWELL: Carla Cuthbert.

DR. CARLA CUTHBERT: Approved.

DR. CYNTHIA POWELL: Kellie Kelm.

DR. KELLIE KELM: Approve.

DR. CYNTHIA POWELL: Kamila Mistry is not able to attend, and Melissa is not here. I move our vote to approve. Annemarie Saarinen.

MS. ANNAMARIE SAARINEN: Approve.

DR. CYNTHIA POWELL: Scott Shone.

DR. SCOTT SHONE: Approve.

DR. CYNTHIA POWELL: Beth Tarini.

DR. BETH TARINI: Approve.

DR. CYNTHIA POWELL: And Michael Warren.

DR. MICHAEL WARREN: Approve.

DR. CYNTHIA POWELL: Okay. I'm pleased to announce that we have five new organizational representatives who are joining us today. We've added two new organizations to the Committee's group of organizations that provide expertise to the Committee; the Association of Women's Health, Obstetric, and Neonatal Nurses, and the Child Neurology Society. Before I introduce the new organizations, I want to thank all of the organizations that submitted applications. We received a number of really excellent applications. Thank you for your interest in the work of the Committee, and I hope that you'll maintain that interest and continue to be involved in the working groups that we have.

So, first of all, I'd like to introduce Dr. Jacqueline Rychnovsky, who is the representative from the Association of Women's Health, Obstetric, and Neonatal Nurses. She is not able to join us today, but the organization has been working to promote the health of women and newborns and strengthen the nursing profession through the delivery of advocacy, research, education, and other professional and clinical resources to nurses and other health care professionals. Dr. Rychnovsky is the Vice President for Research, Policy, and Strategic Initiatives at the Association of Women's Health for OB and Neonatal Nurses. She joined AWHONN in 2016 and is responsible for managing Research Programs, Policy, and Strategic Initiatives for the association. She is a clinician, researcher, and policy advocate with over 38 years of military and civilian nursing experience in caring for women and children. During her military nursing career, she focused on issues surrounding active-

duty military mothers and was the Navy representative on the Tri-service Nursing Research Program, Women's Health Research Interest Group. She is a board-certified pediatric nurse practitioner and fellow in the American Association of Nurse Practitioners, and we welcome her as the representative and welcome the AWHONN association as a new organizational representative.

Next, the Child Neurology Society is the leading professional organization for pediatric neurologists in the United States, Canada, and worldwide devoted to fostering the discipline of child neurology and promoting the optimal care and welfare of children with neurological and neurodevelopmental disorders. With us today representing the CNS, Child Neurology Society, we have Dr. Jennifer Kwon.

Dr. Kwon is a Professor of Neurology at the -- at the University of Wisconsin, School of Medicine and Public Health. She is the Director

of the Pediatric Neuromuscular Program at the American Family Children's Hospital at the University of Wisconsin Medical Center. Dr. Kwon has been serving as a member of the Evidence Review Group and has worked on several evidence reviews for the Advisory Committee on Heritable Disorders in Newborns and Children. She focuses much of her work on improving outcomes for patients diagnosed with rare neurologic diseases by newborn screening. Welcome, Dr. Kwon, and thank you for your representation.

Three of the current organizations that provide expertise to the Committee have identified a new organizational representative. First, on behalf of the Committee, I would like to thank the organization representatives rolling off; Dr. Britton Rink from the American College of Obstetricians and Gynecologists, Dr. Shawn McCandless from the Society of Inherited Metabolic Disorders, and Dr. Adam Kanis from the Department of Defense. I'd like to thank them all for

contributing their time and expertise on a variety of topics. We greatly appreciate your contributions to our discussions.

Taking their places, I would like to introduce Dr. Steven J. Ralston, the new representative for the American College of Obstetricians & Gynecologists. Dr. Ralston is the Chair of OB/GYN at Pennsylvania Hospital in Philadelphia, with an academic appointment at the Perelman School of Medicine at the University of Pennsylvania. He's Professor of Clinical OB/GYN and Vice Chair for Education and Obstetrics at Penn Medicine. He has practiced as a maternal fetal medicine specialist for over 20 years. He currently serves as Vice Chair of the American College of Obstetricians & Gynecologists Committee on Genetics. He has served on the ACOG Committee on Ethics for five years, including three as Chair, liaison to the American Academy of Pediatrics Committee on Bioethics, and to the American Society of Reproductive Medicine Ethics

Committee. He has a BS in molecular biophysics biochemistry from Yale University and MPH with a focus on health law, bioethics and human rights from Boston University, and an MD from Columbia University, College of Physicians and Surgeons.

Next, we have Dr. Georgianne Arnold, the new representative for the Society for Inherited Metabolic Disorders. Dr. Arnold is a Professor of Pediatrics and the Clinical Research Director of the Division of Medical Genetics at Children's Hospital of Pittsburgh. She holds active memberships and positions with a number of professional and scientific societies and currently serves as President of the Society for Inherited Metabolic Disorders. She has over 27 years of teaching, clinical, and mentoring experience. She has been recognized for a number of awards and honors including the Ruth Lawrence Faculty Service Award and the Emmanuel Shapira Award. Dr. Arnold has been recognized in a number of publications including Who's Who in the World,

Who's Who in America, Who's Who of American Women, Best Doctors in America, and America's Top Doctors. She obtained her doctorate in medicine from the State University of New York and completed a fellowship in genetics and metabolism at the University of Colorado Medical Center. Welcome to Dr. Arnold and thank you for representing the organization.

And we have Jacob Hogue, the new representative for the Department of Defense. He's not able to attend today's meeting, so we'll welcome him at the November meeting. Theresa Hart will be representing the Department of Defense for today's meeting. Lieutenant Colonel Hogue is currently the Chief of Genetics at Madigan Army Medical Center located at Joint Base Lewis McCord in Tacoma, Washington. In this role, he is responsible for the medical care of individuals of all ages with suspected or confirmed genetic conditions throughout the region. In addition to his role as a clinician and subject matter expert

on genetics in the military, Lieutenant Colonel Hogue currently serves as the Chair of the Regional Health Command Pacific Institutional Review Board, a member of the Madigan Ethics Board, and he is the Associate Program Director for the Pediatrics Residency at Madigan. He earned his medical degree from the F. Edward Hebert School of Medicine at the Uniformed Services University of the Health Sciences. He completed his pediatrics residency at Madigan Army Medical Center and genetics residency at the University of California, San Francisco. He is board-certified in pediatrics and medical genetics.

So, again, welcome to all of you, and thank you for your participation.

So, I wanted to provide an update on the medical foods report, which the Committee previously accepted. An informational copy with be sent to the secretary within the next few days. The Committee has been following the topic of

medical foods for over a decade and has provided information and recommendations to the secretary in the past. It has been several years since the Committee last reported on medical foods, so the Committee opted to build on previous recommendations to the secretary and offer a review to assess the current landscape of medical foods in the United States.

The report summarizes the state of the science and coverage of medical foods. In the report, the Committee affirms the following principle. Medical foods, as defined by the FDA, should be covered as required medical benefits for persons of all ages who are diagnosed with an in-born error of metabolism, whether specified on the RUSP or identified in clinical practice when the medical food requires authorization by a medical provider and the patient requires ongoing medical supervision and dietary intervention cannot be achieved by modification of a normal diet alone.

And I'd like to thank Sue Berry and the

other authors of this paper and everyone in the working group that participate in this very important document. Thank you.

All right. Our next meeting -- future meetings -- our next meeting will be November 7th and 8th of 2019 in person and webcast, and then following that, our first meeting in 2020 will be February 13th and 14th. The meeting dates through 2023 can be found on the Committee's website.

For today's agenda, our topics for today; first we'll discuss Improving Detection of Newborns at Risk for Homocystinuria and Congenital Adrenal Hyperplasia, followed by a discussion about the RUSP Condition Nomination and Evidence Review progress -- Process. For tomorrow, we'll have the -- a discussion by the International Rare Disease Research Consortium and further discussion on implementation of RUSP conditions report. We'll discuss linking data resources. We'll receive public comments and work group updates.

I wanted to take a moment and talk about

the work group meetings that will be later this afternoon. I have two charges for the work groups this afternoon. One has been more recently added. The work groups have completed a number of projects over the years and contributed a broad range of expertise. I'd like the work groups to do some brainstorming around current gaps, topics, or issues in the field, and discuss ideas for projects that could address these.

Also, in your discussions, consider whether any of these efforts are cross-cutting, perhaps spanning the expertise of more than one work group or if there are any additional areas of expertise needed to help address the gaps, topics, and projects identified.

I'm also interested in feedback from the work groups related to the RUSP Condition Nomination and Evidence Review Process. In particular, the components of the evidence review process the Committee discussed in April and what the Committee will discuss this afternoon.

Tomorrow, each work group Chair or Co-Chair will present a summary of the afternoon discussion including ideas for topics or projects for the Committee to consider and provide feedback on the evidence review process. The Committee will have an opportunity to discuss the ideas tomorrow and then at the November meeting, we'll come back together to consider the ideas generated and identify next steps and possible new projects for the work groups.

Now, I'm going to turn things over to Catharine to go over the DFO slides.

DR. CATHARINE RILEY: Great. Thank you, Dr. Powell, and welcome to everyone that is here with us today and welcome to all those that have joined via the webcast across the different states. We welcome everyone. So, I'll start with some standard announcements.

This 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 community activities are governed by the Federal Advisory Committee Act or FACA, which sets the standards for the establishment, utilization, and management of all Federal Advisory Committees. As a Committee member on a Federal Advisory Committee, you are subject to the rules and regulations for special government employees.

I also have standard reminders to the Committee I would like to go over with regard to ethics and conflicts of interest. I wanted to remind the Committee members that as a Committee, you are advisory to the Secretary of Health and Human Services, not Congress. For anyone associated with the Committee or due your membership on the Committee, if you receive inquiries, please let Dr. Powell or I know prior to committing to an interview.

I also would like to remind Committee

members that you must recuse yourself from participation in all particular matters likely to affect the financial interest 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 Health and Human Services 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.

So, as a Federal Advisory Committee, 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 and announced here at the meeting. For this meeting, in the Federal Register, we noted that there would be two public comments sessions, one today and one tomorrow. We received requests for six public comments, so

we'll hear some of those today and some tomorrow. We also received one written comment, and that was provided to the Committee members before the meeting, so they all have that.

Any further public participation will be solely at the discretion of the Chair, Dr. Powell, or myself as the Designated Federal Official.

Before I move on, do I have any questions from Committee members? Okay.

So then, just a little bit of housekeeping. For visitors, we only access to the pavilion, which is this room, the cafeteria, which I think most of you are familiar with, and this main area on the fifth floor, and the meeting room areas. All other areas of the facility are restricted and require an escort by a HRSA staff member, and there are no exceptions for this. If you need to leave and re-enter, you will be required to go through security screening again, and you will require a HRSA escort to meet you at the security -- the main security entry point,

which is in the front of the building where you came in this morning. For the lunch break, we will have a HRSA staff member there before and after the lunch break to provide an escort if you want to leave during lunch and come back.

So, visitors are not allowed to take any video or photography in the building, in particular near the front or the security entrances. In case of an emergency, we ask that you please exit through the front door --, so that's where you came in for the security check point -- and meet in the parking -- parking pad or parking lot across the street and to the left. The HRSA staff member escorts will have a list of everyone that is signed up for attending the meeting and will assure everyone has been accounted for. Security asks that you please not take any nonessential items with you, as this may delay exit and reentry into the building.

And with that, I'd like to turn it back over to Dr. Powell. Thank you.

DR. CYNTHIA POWELL: Thank you, Catharine.

DR. CYNTHIA POWELL: Next, we're going to be hearing from Dr. Carla Cuthbert from the Centers for Disease Control and Prevention. She is an ex-officio member of this Committee and will be talking about Improving Detection of Newborns at Risk for Homocystinuria and Congenital Adrenal Hyperplasia.

To give you a little bit of background on this, at the last Committee meeting in April, we heard from several public comments about screening methods and how to improve newborn screening for congenital adrenal hyperplasia and homocystinuria. The CDC has been working on screening methodologies for both of these conditions. I asked Dr. Cuthbert, who is Branch Chief of the Newborn Screening and Molecular Biology Branch at the CDC, to provide an overview of the activities they are working on to improve risk assessment and provide an update specifically on screening

methodologies for homocystinuria and congenital adrenal hyperplasia. We anticipate having more in-depth presentations about these methods at future meetings. And, thank you, Dr. Cuthbert, and go ahead.

DR. CARLA CUTHBERT: Thank you, Dr. Powell. It's a pleasure to be able to have an opportunity again to address my fellow Committee members and to people of the public. I'm -- today, again, we're going to be speaking about some of the efforts that we have been engaged in within our branch, and I just wanted to again just repeat what -- what Cindy said. What I'm going to provide is just a very basic overview. I do have some wonderful scientists working in my branch, and it's wonderful being able to have some of my biochemists speak to the branch when the molecular biologists and listening and their eyes sort of glaze over and visa versa. But it's very, very important because there is really a bit of interconnectedness in terms of what we're actually

trying to do with creating methods, with improving methods so that they are relevant to state programs and so that the states can actually just be able to learn from us and be able to adopt and implement. So, this is not really going to be a comprehensive discussion about methodology, and those of you who are not biochemists would probably breathe a sigh of relief, unfortunately. So, again, it's not a detailed discussion of ongoing projects. I just want to be able to give you a big of a highlight of things that are happening and that are addressing detection for homocystinuria and CH.

So, I just wanted to highlight again what we do. I know that you probably heard me speak and talk about some of the things that we're doing. For some of you -- some of you may know that we got a bit of increase in funding last year. So, we've been looking at how we could really effectively use this funding to help states along. But really, the core sets of activities of

what we do to support states really remain the same.

One of the big things that we do is that we're involved in method development. We create quality assurance materials, and for those of you who don't know what that is, we create blood spots that look like -- that mimic samples of affected newborns. We create those with the -- with the biomarkers in mind. One of the things that we have done is just over the last couple of decades is that we -- we chose the specific key markers. Now, we're looking not just at specific markers, we're looking at panels of biomarkers that we want to be able to include. So, that's requiring a little bit of changes on our part, but we really do want to remain flexible to the changing needs of our programs.

With respect to -- just to go back to the previous point with new development -- method development -- we do -- as we understand whether or not new conditions are to be added, we -- we

have scientists that are designated to work on some of these things. But one of the things that we really want to be able to do specifically over the course of the upcoming decade, 2020 to 2030, is to really take a look at some of the conditions that we currently have to see how best we can make improvements to them. So, we have been engaged in that process.

Down to the third bullet, we provide support, and this is financial support for programs, to implement screening for recently added conditions for the Recommended Uniform Screening Panel. We remain very close with the programs and really help them along if they have any technical issues. Once they've implemented, we remain in contact with them because of our quality assurance programs, so we know if something is not -- if performance is not what it should be, and we work with them either to bring them to the CDC to provide training and education, or, if it's needed, I can send one or two of my

staff onsite to be able to help them along and help with their -- their training and help to troubleshoot some of their issues.

So, that's really the big picture of what -- of what we're doing, and in the context of -- of homocystinuria and congenital adrenal hyperplasia, we have ongoing activities that are just a part of our routine strategy to improve some of these tests.

So, just to remind you about homocystinuria, the -- the -- the enzyme that is deficient is cystathionine beta-synthase. This, of course, leads to an accumulation of homocysteine and secondarily methionine. The biomarker that we screen for in newborn screening is methionine. But, unfortunately, methionine is not a unique biomarker for -- for homocystinuria. There are other causes that can result in increases in methionine in newborns. It is seen in increased liver disease, hyperalimentation, and some other remethylation disorders can result in

increases in methionine. Clinically, these patients present with life-threatening thromboembolism, seizures, developmental delay, skeletal changes, and other -- other clinical presentations as well.

So, one of the big pictures that we have been thinking about for quite a while, and which was brought up with public comment, was how can we again create a second-tier test for homocysteine. We would need to include some other biomarkers as well because elevations of homocysteine are also seen with cobalamine defects, so, again, we have to be very thoughtful of what we would actually do.

And, of course, the big question is being able to create a first-tier test for homocysteine. That presents its own challenges, because the use of the reducing agent associated with the tests that we currently do have result in ion suppression for some of the biomarkers, so it makes it quite difficult.

So, again, some of the -- the ideas brought up by Danae, Elizabeth, and Margie. When they spoke, they again wanted to bring it to everyone's attention that many cases of patients with classical homocystinuria are being missed. Methionine is the current marker, not homocysteine. Homocysteine would be a much more appropriate marker, of course. Cutoffs in many cases to avoid some of the false positives are set a bit too high. So, again, what they mentioned was the benefit of reducing current cutoffs for methionine and the inclusion of second-tier tests for both homocysteine and methylmalonic acid. Of course, there was also a discussion about developing a first-tier test that includes homocysteine.

For congenital adrenal hyperplasia, the enzyme of note here is 21-hydroxylase. That is the cause of most cases of CAH. Clinically, these patients' screening will identify classic and severe forms of the salt-wasting and simple

virilizing forms of CAH. The newborn screening biomarker is 17-hydroxy progesterone. The testing platform most commonly used is the fluoroimmunoassay or FIA. And again, as with methionine, elevations of 17-hydroxy progesterone are also seen during -- as a result of -- of stressful delivery, immaturity of adrenal glands, and of course there is an issue with a lack of specificity with this assay with other steroid intermediates.

So, again, this is something that we have known and one of the approaches, of course, is adjusting the cutoff and using second-tier tests. In many cases, it would be a steroid panel that many of our programs would use. However, there are still instances of false positives and false negatives with current algorithms, and so this remains a concern.

Dr. Emmanuele Delot, I believe, did have some comments, and again, he mentioned some of the things that I just mentioned. He also indicated

that the Endocrine Society published clinical practice guidelines for the management of CAH. In those guidelines, there was a section on newborn screening with a call and a hope for improved methodology, standardization, and other things to really enhance how these newborns are detected so that they can be routed into appropriate management.

So, that's a bit of the background. I'm just going to run through a couple other things that we're doing at CDC. Our branch is sort of broken into the biochemical group, the molecular group. So, I'm going to be talking to you about four different methodologies that are being developed and are at different stages in development. Some of them have already been validated and are in use.

But some of our thoughts in terms of trying to address some of these issues -- so, I'll just go right on.

The first method is a second-tier

screening method that includes detection of -- of homocystinuria, methylmalonic acidemia, propionic acidemia, GAMT, and MSUD. And I know that you're not really going to be seeing any of this. Is there a pointer with this? Yes. But these are a number of the biomarkers. And again, this is just to indicate a level of separation with some of these. Again, the rationale behind a grouping of second-tier biomarkers is that we're all dealing with rare disorders. Most of the programs will have a certain low level of screen positives. So, again, if you have a single test that would be useful for being able to do second-tier screening for a number of difference screen positives, that would be in the best interest of the workflow of the programs

So, you'll see that we're trying to do a lot of combinations and multiplexing in this particular -- in this way. So, yes.

So, this is one of the tests that has been developed. This test, in particular, is

being taught to states programs. We have an annual mass spectrometry course, and as part of their training, they do learn how to -- how to develop this, and of course, there is the -- I know you can't see it -- it's that yellow text up here. This peak right here is the homocysteine peak that is able to be detected using this method.

Method number 2 is also another second-tier screening method. This is for congenital adrenal hyperplasia using a steroid panel. Again, there are a number of programs that probably have adopted this already. Again, being able to bring it up for us within CDC allows us to be able to teach and to demonstrate how to do these -- these assays and to be able to do troubleshooting with our programs. So, this is something that we have been working on, and we're looking forward to being able to teach the next group of newborn screeners that will be coming to our annual MSMS course in 2020.

We have another second-tier screening method. This one we call Universal, and, of course, I talked to my mass spec person, and I said, well, it's not really universal, but it is -- for the most part, it's the ones that give us problems. So, for the most part, again, being able to expand out the different kinds of biomarkers using different platforms. So, this is again a unique kind of -- of -- of column that is being used to be able to separate out the amino acids, acylcarnitine, and so on in a single assay. This, to our knowledge, is not currently being done. But again, the advantage here is that we have some of the first-tier biomarkers together with some of the -- the second-tier biomarkers. But this is, again, a really much more comprehensive single assay that can be used with most of these programs.

So, this is still under development as we get more and more successful in this. Again, we're looking for our tests to be much more robust and

to be able to ensure that we can put this in the hands of our programs and have them consistently get the right results. So, these are things that we will be looking for in the future. But this is promising and we're -- we're looking to see how best we can develop it into something that's useful.

The fourth method -- the fourth biochemical method is the one that is meant to include both first- and second-tier biomarkers. And again, the idea is, you know, we are -- we're going to be adding more and more conditions onto the RUSP. We need to have something that has a bit more flexibility. And so, my -- my mass spec lab chief has been looking at doing -- using this platform that’s an ultra-high throughput on a chip mass spectrometry approach, and again, this is meant to do a couple of things in addition to including first- and second-tier biomarkers. We do have -- sorry. Let me go back here. We do have homocysteine here. This one does not have,

at this point in time, CAH biomarkers. But again, they are just looking to add more and more biomarkers just to see how this -- how these assays are going to work. But we do have homocysteine here. One of the nice things about this is that it's able to actually separate out isoleucine, leucine, and allo-isoleucine and also C3DC and C4OH. And so, being able to have a single platform again where you don't actually need second-tier tests, that's great. And being able to incorporate some of these secondary biomarkers that would be necessary for us to improve the detection for homocystinuria and CAH, those are really helpful things.

So, these are things that are ongoing. We're looking really very broadly at a number of the conditions that are giving us problems and just conceptually ensuring that we can have both primary biomarkers as well as some of the secondary -- the known secondary informative biomarkers included in single tests.

So, this is definitely still under development. Of course, all of the things that we need to think about include, you know, throughput, how flexible is it for a state to bring it on, costs. All of these things need to be considered. So, again, these are proof of principle studies that we hope to be able to adopt and to hopefully implement within a public health setting.

So, I had mentioned that we do have training. We have training once a year. I'm constantly asking both APHL and my staff whether or not they can navigate having two a year because there is a very significant need. We have a number of programs asking to participate in these programs where they learn the hands-on applications of these studies. But this is what we actually do, and we may get as many as 30 or so applicants each year. We can only take about 10 to 12. They are a combination of classroom and -- classroom sessions on second-tier screening, but there is a very heavy hands-on laboratory

component where they really engage in best practice within the laboratory.

Another one of the benefits of this is that they really develop relationship with our staff so that they feel comfortable when they have problems to be able to have conversations with -- with our people. And again, I'm happy to send programs -- some of my staff over to help, especially with the development of some of these -- some of these tests.

And I do also want to mention that even -- even prior to the public comment, one of the things that I had conversations with some of my senior staff with the mass spectrometry group was that I really, really wanted to focus over the course of these, like I said, these next ten years to implement a second-tier testing in all of our programs, and that is -- that's something I really would like to do as an agency program goal.

So, we're looking at how that could actually happen and, yes, we're hoping for the

best for that.

So, I'll just wrap up quickly with the next couple of slides which just talk about a brief study that we did in collaboration with our colleagues in Minnesota to develop a Molecular Approach to Enhance Detection of CAH in Newborns at Risk for Congenital Adrenal Hyperplasia.

So, again, the big issue was that there are both false positives and false negatives for newborns with -- that are being screened for CH. There are a number of external factors, as we indicated, that can cause an elevation of 17-hydroxy progesterone. And so, the challenge is -- and again, these are molecular biologists thinking about this -- you know, we need to have an alternative newborn screening test that is not influenced by the timing of the sample, prematurity, or birth stress, or cross-reactivity of -- of other steroids. And so the thought is, could we increase sensitivity by reducing 17-hydroxy progesterone cutoffs to eliminate the

false negatives and consider a molecular second-tier test to maintain screening specificity. And we were very -- very happy to be in partnership with our colleagues in Minnesota. We see the grant co-investigators on this slide, and they put together a proposal and they got some funding from the March of Dimes. And again, this grant title was to address whether or not molecular testing could improve newborn screening performance and outcomes for CAH. Like I said, the co-investigators are listed here.

So, this slide describes responsibilities and roles. The University of Minnesota and CDC were responsible for defining a Minnesota population variant for the CYP21A2 gene and to subsequently create a variant panel. There were families that were identified within the Minnesota population who had CAH, and they identified a total of 22 pathogenic variants together with the 30KB deletion alleles.

CDC was responsible for creating a high-

throughput molecular assay for the newborn screening laboratory. We use the Multiplex Allele-Specific Primer Extension or ASPE assay using Luminex Technology. This was transferred to the Minnesota group so that they could do the pilot test to evaluate the molecular assay.

Just in summary here, once we created the panel that was transferred, they did essentially a one year -- a study using one-year samples, so 72,000 samples were screened. They identified the one known true CAH positive using this algorithm that had the first-tier test together with the molecular tier. There were two CAH babies that had been missed by the current screening algorithms. One had been missed by the primary assay cutoff and the other was missed by the second-tier assay. And this particular assay identified all of these.

Any other cases identified were confirmed by sequencing at CDC, and they found that they correctly identified all of the deletions. They

had to make a bit of an adjustment to -- to the probe and just redesigned and were able to create a panel that they were -- they were fairly happy with.

Just in summary then, this represented a novel state, federal, and academic collaboration as a model for future newborn screening molecular test development. They established a comprehensive CYP21A2 panel for the Minnesota population and this, again, could be used for other populations. Again, it would be very helpful to ensure that you -- you knew the populations within your -- your own -- your -- your population itself. The molecular CAH results certainly will require in-depth reporting, infrastructure development. There were, you know, samples that were identified just with the one variant. So, there is the potential for a high false positive rate, and ironically there were some that had multiple variants on the same chromosome. So, there is a need for developing an

assay for phasing to eliminate the need for family testing.

So, again, there is a lot to be done. This was a really thoughtful assay -- thoughtful collaboration, and we really do appreciate our colleagues in Minnesota for being able to work with us in that regard.

So, this is a summary of -- of some of the things that we're doing specifically -- I'm sorry, this is the acknowledgements of the people who were involved in that study. But this, again represents some of the biochemistry, i.e. the mass spec-related assays together with some of the molecular tests that we're actually using to address specifically enhancements of disease detection for patients with homocystinuria and CAH.

That's all I've got to say. I'd be happy to take any questions. I know that we're a little over time.

DR. CYNTHIA POWELL: That's okay. Thank

you very much, Dr. Cuthbert. And, yeah, we're going to open this up to questions and comments from the Committee members first and then from the organizational representatives. So, if the operator could please open the lines for Committee members and organizational representatives on the conference line, and you're welcome to stay up there or you can go ahead and have a seat. Thank you.

So, I want to thank Dr. Cuthbert. I also want to thank the families, clinicians, and researchers for bringing this important topic to the Committee's attention during the April meeting. I'm happy to hear that the CDC is working on evaluating the sensitivity, specificity, positive predictive value, negative predictive values of current screening methods. The Committee needs more information on the current state of the science to determine if and how they want to address the issues raised at the April meeting related to risk assessment for

homocystinuria. So, this is an important first step. We'll continue to follow this issue and bring in experts to present to the Committee at future meetings.

And at this point, I see Mei Baker.

DR. MEI BAKER: Colleagues, wonderful presentation. But the one thing you said that actually caught my attention is combined first-tier, second-tier markers together. So, you used the example leucine, isoleucine, and allo-isoleucine. I was thinking that the future direction, did you foresee if isoleucine can get a first-tier panel -- I mean analyze it, do you even still need a leucine isoleucine? Because isoleucine gives us false positive, because if you have a liver function problem, you have other things. If you have isoleucine to use, you need leucine -- I mean allo-isoleucine, you don't need leucine isoleucine, right?

DR. CARLA CUTHBERT: Let me try to understand that you're saying. Are you trying to

say should we put allo-iso on the --

DR. MEI BAKER: I thought you were trying to put the first-tier marker, right?

DR. CARLA CUTHBERT: Right. So, technically it's a second-tier. I mean, you'll see -- they're iso bars. So, you're looking for allo-iso, but they -- they come out at the same peak. So, you actually have to do a secondary test to determine what's under that particular peak. So, allo-iso and leucine. So, to avoid doing a first-tier and a second-tier, we put them together. Am I not getting what your question is?

DR. MEI BAKER: I hope I understand correctly because I think the concept that you're trying to introduce is a combined first-tier and second-tier?

DR. CARLA CUTHBERT: Correct, yes.

DR. MEI BAKER: If -- for allo-isoleucine, you can put first-tier --

DR. CARLA CUTHBERT: Yes.

DR. MEI BAKER: -- then potentially you

will not need a leucine isoleucine. That's -- I thought that this was a very good direction to go, right?

DR. CARLA CUTHBERT: Sure. Yes, yes. I man, allo-isoleucine is the biomarker you want to look at for MSUD. Absolutely.

DR. CYNTHIA POWELL: And on the phone line, we have a question from or comment from Scott Shone.

DR. SCOTT SHONE: Hey, Carla. So, excellent presentation, and as always excellent work by your team. So, thank you so much for sharing it. I'm trying to bring this back to sort of like a broader system view of the implementation of this work. We're going to hear some more, I think, over the next day or two on implementation of disorders, but I'm also thinking about this in terms of these types of assays and their ability to make what we do more specific and sensitive.

One of the facilitators that's often

highlighted is the availability of a commercial assay or even FDA-cleared assays and obviously this is laboratory developed, and you're doing a great job with training people. But do you see potential barriers with states being able to and programs being able to bring these assays up and running and -- and combining that with perhaps the commercial options that they're using as first-tier, and do you know of any vendors who are looking at perhaps bringing on second-tier commercial tests that would help, you know, build into what we're hearing from the system -- our facilitator's implementation?

DR. CARLA CUTHBERT: So, one of the big reasons that we actually want to publish on -- on these tests is so that vendors can look at it, and they can choose. Certainly, we cannot approach anyone and sort of ask them to do this. We hope that they're just paying attention.

So, in terms of whether or not we know whether or not anyone is actually doing this, no.

I think that as we look at the future of newborn screening, we know that we have to consider ways to combine these markers and perhaps have better and more relevant markers on our tests. We know that this is going to be difficult to adopt. So, you know, I certainly do want to emphasize not necessarily for the states who already know this, but for those of you who are listening, these -- these things are difficult. And, you know, while it might work well in our hands at CDC as we're doing many tests over and over, we really do have to get this into the hands of state programs. And, you know, we're -- we're not entirely discouraged if we get it into a state's program's hands and then it still requires tweaking. We really do want to figure out how we can actually create the best possible outcome for states.

So, Scott, you know better than I do that many of things require money. Speaking to states, many of these things also require people who are technically savvy -- technically capable of doing

these -- these kinds of tests and troubleshooting. And hence, you know, again wanting to make that we have funding available -- we don't yet. So, you know, this is still sort of things that are aspirational. And -- and we know that somehow we have to modify our training approach so that we can ensure that there's technical capability within your -- within your programs.

DR. SCOTT SHONE: Right, Carla. I just want to, I think, just funding, as you said, is just one thing, the expertise is another as this gets more complex. I just -- you know, we're already in this environment where people say if I was born in this state I'd get this panel and that, and we're, as a Committee, trying to think about addressing that. I just don't want to now get to well there are fewer false positives in this state because they go with this, and I had, you know, and I endured this path of the screening process. And so, I think as we're going this way, which I think is -- is excellent, but we need to

be cognizant of setting up another one of these challenges that, as a Committee, we need to be -- you know, we have the opportunity here to think about it as we're looking toward implementing and spreading this -- it's not just now disorders, it's second-tier, it's third tier, it's whatever, and that sort of class system of programs. We need to be aware of what we're thinking about and how do we -- and not that we shouldn't do it, but how do we help keep that from happening.

DR. CYNTHIA POWELL: And, I'm sorry, I forgot to remind everyone to please state your first and last names when you are asking a question or providing a comment so that we can ensure proper recording of the meeting.

Next, Melissa Parisi.

DR. MELISSA PARISI: Hi, Melissa Parisi from NIH. Carla, I just had a question about the pilot program for molecular testing for CAH, and you showed the diagram of the 72,000 samples that were screened, and then when you did the molecular

evaluation, 70 were identified with at least 2 variants, which is a fairly high number. The true positives within those 70 was only 3, if I understand correctly. So, as you stated, that reflects either, you know, potentially our need to learn more about this gene and variants and their pathogenicity as well as the phase, as you mentioned, of whether or not they're on the same allele or different alleles. And I'm just wondering if you have some plans in the works to try to define that molecular analysis to make it more robust.

DR. CARLA CUTHBERT: Yes. Yes and yes. The -- there are many -- I think in one case there were many variants on one allele and one chromosome, which was astounding. Chris Green, who is the lead on this project, presented it to my boss, who is not a molecular biologist, and that just blew his mind. So, it just -- it just requires us to be very thoughtful about how we do it. Just because you find a variant or two, it

doesn't mean that this person is at risk for this disease.

DR. CYNTHIA POWELL: Any other comments or questions from the Committee members? So, we'll open this up to the organizational representatives. Georgianne.

DR. GEORGIANNE ARNOLD: Am I -- okay. Georgianne Arnold, Society for Inherited Metabolic Disorders. Was there any interest in opening this up to genes for low methionine homocystinuria like cobalamin disorders?

DR. CARLA CUTHBERT: Yes. A lot of this depends on how low can you go, right? So, with these new platforms, their ability to -- to detect low levels, we hope will be improved, and as such, being able to identify these low cutoffs is what we hope. That's something that we'll have to look at.

DR. GEORGIANNE ARNOLD: Yeah, know that they were looking at trying to this with lower cutoffs, but I was wondering if the lower cutoffs

plus the DNA would be -- is something they were thinking about working at. Okay.

DR. CARLA CUTHBERT: Yes. So, again, everything is dependent on resources, and, of course, within -- within our branch, we have so many projects. So, these are things that are on our radar. They're not actively being engaged on right now. But these are things that we're thinking about, Georgianne. Thank you. That's a great question.

DR. CYNTHIA POWELL: Susan Tanksley.

DR. SUSAN TANKSLEY: Susan Tanksley, Association of Public Health Laboratories. Thank you, Carla for the presentation. I was wondering if there had been a comparison of the two CAH second-tier assays, the molecular versus the LC-MS/MS and how that -- how they fared.

DR. CARLA CUTHBERT: I think I might have to defer to Amy Gaviglio, because Amy is from Minnesota, and I think I will have to bow out to her.

MS. AMY GAVIGLIO: Yeah. Amy Gaviglio, National Society of Genetic Counselors. Yeah, we did look at performance between -- between the two, and it's a bit interesting, because we did pick up so many single-variant findings. Our carrier frequency was 1 in 13, which was much higher than we expected. And so, we had to think about -- about that. There was also the issue with multiple variants, and we had one child with eight variants who ended up being trait. So, it was a bit hard to actually look at -- look at performance metrics in terms of what are you going to call a positive result. Is it a one-variant finding or is it a multiple-variant finding, and are you able to do phasing before calling -- calling that out? So, I would say that we were able to pick up our false negative cases, which was good, but if we're going to be calling out all of the single variants and calling those as false positives, then that becomes a different situation. So, it was a bit hard to kind of

compare straight -- straight with like a steroid profile or an extracted 17OHP.

Interestingly, you do see a shift, whereas we typically saw most of our false positives, as Carla mentioned, in the low birth weight NICU population, you see it actually shift now to all of the single variants are primarily in your well-baby population, which makes sense given that their 17OHP in the NICU isn't because of CAH. So, you also see a different shift in population.

DR. CYNTHIA POWELL: Mei Baker.

DR. MEI BAKER: I just want to have a follow-up -- oh, Mei Baker, Committee member. Follow-up on Georgianne's question about low methionine. So, two things I want to make comments. First, in the newborn setting, identify low concentration is more challenging, just when we talk about using succinylacetone for OTC. It's just very hard to do, overlapped with so many different scenarios.

Second is when we talk marker, I just --

what comes to my mind is we need to think about the marker associated with disease. Is the disease justified to be identified? You know, newborn screening -- are you screening disorders or are you screening differentials? So, we have to keep this in mind.

DR. CYNTHIA POWELL: Sue Berry.

DR. SUSAN BERRY: So, the question I had was, Amy, could you say something about the pseudo-allele and how that impacts detection.

MS. AMY GAVIGLIO: For?

DR. SUSAN BERRY: For CAH.

MS. AMY GAVIGLIO: I believe the assay takes care of that.

DR. SUSAN BERRY: Okay. I just don't about the methodology well enough.

MS. AMY GAVIGLIO: I don't remember -- yeah, yeah. No, I mean --

DR. SUSAN BERRY: So, that's not --

MS. AMY GAVIGLIO: The gene is exceedingly in a complex region.

DR. SUSAN BERRY: Right.

MS. AMY GAVIGLIO: So, it causes a host of issues, which is why we kind of have a multistep assay. But we -- yeah, it -- it -- the assay seemed to be fine --

DR. SUSAN BERRY: Great. Thank you.

DR. CYNTHIA POWELL: Any other questions from --

DR. DEBRA FREEDENBERG: Yeah. This is Debbie Freedenberg.

DR. CYNTHIA POWELL: Yes, go ahead, Debbie.

DR. DEBRA FREEDENBERG: I'm an Academy of Pediatrics rep. Carla, thank you so much for that great talk. My question is, do you foresee any differences in utilization and implementation in these newer methods between one-screen and two-screen states?

DR. CARLA CUTHBERT: I'm -- I'm not sure. You know, if we have an opportunity to be able to partner with one-screen and two-screen states as

we consider what this would look like, I think that would be helpful to identify any unique challenges that two-screen states would have. But -- but again, I -- we're at the very early stages of trying to identify first a test that might be useful. There's going to be a whole other series of questions once we start doing the clinical validation and looking at the utility within newborn screening environment. But thank you for asking that, Debbie. That's going to be an important question.

DR. CYNTHIA POWELL: Any other questions from those on the line? All right. Thank you, everybody. Thank you again, Carla.

DR. CYNTHIA POWELL: Thank you, Catharine. We opened up the comments about the nomination, the RUSP Condition Nomination and Evidence Review Process from the broader community of stakeholders, and the Committee welcomes feedback from stakeholders and blocked off time on today's agenda to hear feedback specific to the

RUSP processes. We're going to have another public comment session tomorrow. And we have several individuals who signed up to provide public comment. And we have a general -- first, we have, let's see, a general public comment from Margaret McGlynn, who will be speaking today about homocystinuria.

MS. MARGARET MCGLYNN: Thank you, and thank you for letting me speak today, as Catharine was flexible, because I can't be here tomorrow. It's not specifically related to RUSP, but it's a condition that's on RUSP. But, thank you.

I met many of you in April when I presented at this forum along with two others. I'm Margie McGlynn, and I'm the co-founder and President of the Board of HCU Network America, which is an advocacy organization I founded along with Janae Bartke, who you met in April, in honor of my two sisters who lost their lives to HCU. My hope is that no family in the future has to suffer from losing a child or an adult like mine did to

this disease.

So, I'm here today to follow up on the comments that I had made in April, and I thank Carla for summarizing my comments. I'm flattered to be quoted by the CDC, Carla. But I also thank Carla for the work of her and her team in this important area on improved assays to detect HCU.

Since the last meeting, we've had the opportunity to talk to some of the states about their programs and their experience with detecting HCU, and almost everyone told us that they believe that they are detecting all patients with HCU, but they did acknowledge they don't have the feedback loops to know whether that is really true. Well, unfortunately, we don't believe that they're detecting all of the patients, and that's based upon not only the estimate in the literature that 50 percent of patients are missed by the current approach, but also a published abstract on medical claims data specific for classical HCU, and I know many I've talked to about this said oh it's an

upcoding that occurs, but they have other clinical sequela which are consistent with HCU, and they're being treated with vitamins and other products that are known to be used for classical HCU.

There is also analysis recently completed that will be published of a genetic database that looked only at the specific defects that are shown to cause disease. Both of these sources would suggest there are even more than 50 percent of patients who are missed, many of whom suffer later in life from premature stroke or blood clots.

But the most important evidence we have, we mentioned last time, are the patients who tell us they were missed at birth, and we have identified 22 patients across 12 states that were diagnosed in states where newborn screening was in place at birth, but they were not detected until later in life due to clinical issues. All 22 were pyridoxine non-responsive, which is the more severe type. And we believe we've only scratched the surface. You've heard about a few of these

patients last time -- I won't go into details -- but to remind you, a little girl from Montana diagnosed with a blood clot at age 3. You heard from a mother of a boy in South Carolina diagnosed after uncontrollable seizures spending 29 days in the ICU in a medically induced coma. And most tragically, you heard from us about a little boy in North Carolina diagnosed at age 6, who suffered a blood clot at age 8 on his way home from a baseball game and unfortunately died after a week in the ICU.

We know that every one of you involved in this effort and all of the staff and leadership at the state programs and state labs want to detect all patients at birth to give them the best chance of getting optimal care and avoiding clinical sequela. And, as Carla said, we all believe the best long-term solution is to enable a first-tier screen of homocysteine. So, we're hopeful for the efforts you have underway. We are also offering grants through our global grants program for the

development of a primary HCY test.

But, we also believe that in addition to improving newborn screening, there needs to be ongoing screening past the newborn stage to detect those older children and adults who may not have had elevated levels at birth, and we hope to work with some of the organizations represented at this meeting to figure out how to best approach that.

So, while that first-tier screen may be years away, we are hopeful that there are tiered testing approaches in place today that can be evaluated by the Committee and can be implemented in the near future. One of those approaches was proposed more than ten years ago by the group at the Mayo Clinic, and that was published in JIMD in 2007, where they recommended lowering methionine cutoff and then using the second-tier test to assess homocysteine and MMA using the same dried blood spot. Their approach included a lower cutoff for methionine, simultaneous measurement of methyl citric acid, along with homocysteine and

MMA, and that's published in Clinical Chemistry in 2010. And this enables better detection of not only CBS-deficient homocystinuria, but also the question asked earlier of cobalamin defects, methylation disorders, propionic acidemia, and remethylation disorders, and it avoids the impact of false positives on families.

As many of you know, Mayo also implemented bioinformatic tools known to the Committee as CLIR in order to further reduce the overall screening cost and reduce the need for second-tier testing.

A few states in the US are already taking advantage of this approach, and some have contracted with the Mayo Clinic to provide the second-tier testing.

Other countries have also picked up on the two-tier screening approach, as I mentioned at the last meeting, and most recently a publication by EHOD or the European Network and Registry for Homocystinuria and Methylation Defects reiterated

the importance of this approach and has a lot of the data that came from programs that came from programs that justified why a conversion to second-tier approach made sense.

Now, we know this is a complex area. We know the resource issues and complexities that programs are dealing with. But we would urge the Committee to take on this effort, which was described by some at the last meeting as low-hanging fruit. While we would love to pick that fruit and we would love to come up with a better approach to help this patient community. So, we encourage the Committee to evaluate these tiered approaches being utilized in the US and internationally. We have connected three experts at Catharine's request to the Committee, and all are willing to engage with the Committee and to present their experience and that includes both the US and two countries internationally.

So, we encourage the Committee to support the ongoing work of the CDC. We've also consulted

APHL and ACMG on this effort, and we thank them for their input. And we also encourage NICHD to get involved, as we believe that their mission to refine and improve the analytical approach to NBS would make them an important contributor to this effort.

So, again, on behalf of the HCU community and especially those families who have patients missed by newborn screening, we thank the Committee for listening. We really do. I was very impressed when we had comments from the outgoing Chair, incoming Chair, and many Committee members both publicly and informally to Danae and I after the April talk. It's clear that you really do want to hear from the patient community, but most importantly, you listened to us, and action was already underway but is being further encouraged by the Committee and so, we offer our support to you as you embark upon this effort. We urge you to take action to address this low-hanging fruit and to come up with a solution that

can be implemented within the next few years. Thank you again.

DR. CYNTHIA POWELL: Thank you, Margaret. Thank you for emphasizing the importance of this situation and the importance of the Committee to continue work in this area. We look forward to having additional presentations at our next meeting from experts from not only in the US but hopefully from others internationally and continue this work.

So, next up, there will be three individuals who signed up to provide public comments on the RUSP Nomination Evidence Review and Evaluation Processes. First we have Joseph Schneider.

DR. JOSEPH SCHNEIDER: Good morning and thank you. Thank you very much. Good morning. I'm Joseph Schneider. I'm a practicing pediatrician in the newborn nursery of Parkland Hospital from UT Southwestern. I'm a member of the Texas Newborn Screening Advisory Panel, Chair

of the Texas Medical Association, HIT Committee, and a former Chief Medical Information Officer of a few large health care organizations over the past 20 years. I'm also a retired businessman who graduated from medical school at the ripe old age of 43.

I've been on the Long-term or Longitudinal Follow-up Committee for about 18 months and we still have -- I still have a lot to learn. I'm commenting today because I think we're about to talk about how to change the newborn screening candidate process and therefore the program as a whole.

I see the newborn screening program as an investment. Like any investment, we need to know its long-term effects. In many cases, simply screening and doing limited follow-up is not enough. Newborn screening saves lives, but I believe we want to understand the long-term physical, psychological, and social impacts in these lives so that we can continue to improve

them. Much less has happened in cystic fibrosis and in the separate field, pediatric oncology. With this background, I'd like to stress three things as the Committee considers changes.

I recognize that the Committee can't make these changes directly, but I think that you can set the vision. First, to achieve this goal of continuous improvement, we need to create a learning health system that starts with newborn screening patients. Simply put, the learning health system is where every activity leads to improvements. To do this, we need to have a culture of seeing virtually every patient as continuously contributing to research and quality improvement. Today, patient visits are recorded as transactions for patient care and billing. Changing our culture to where each visit and the time between visits provides data for research and quality improvement is hard, but it's needed. So, creating a vision of newborn screening and follow-up as the start of a learning health system is

point number one.

My second point is that we need to standardize our data, data collection processes, reporting, and analytics nationally so that we can make it efficient and electronic. If we do this, we can get the attention of EMR and other health information technology vendors who will build in these capabilities. But if each physician, each clinician, each children's hospital, and each state program persists in doing things their own way, we'll never get there, because EMR vendors and IT groups have many other important things to think about. So, national standardization is point number two.

My final point is that we need to get patients and parents involved and to provide them affordable and easy-to-use tools that they can use to contribute to this continuous research and quality improvement effort, and we need to foster their trust and support. I've read the law, and it's not the job of the Advisory Committee to do

what I've described. But I think it is the responsibility of the Committee to create a vision -- to create or recreate a vision of the future and advocate strongly for these three points; learning health system, data and process standardization, and patient/parent involvement.

It's said that a journey of a thousand steps starts with one step. Newborn screening has come a long way, and I deeply appreciate that certainly as a physician that I am. But we still have nearly a thousand miles to go. Let's take that first step today, and let's take it in the right direction. I hope that we can -- as we consider modifications to the candidate review process and the program, we can keep these three points in our vision. Thank you very much for the opportunity to comment, and you have a copy of this.

DR. CYNTHIA POWELL: Thank you, Dr. Schneider.

Next, we'll hear from Vikram Pansare.

Are you on the line? No? Okay. We do have hopefully Heidi Wallis on the line. Are you ready to present?

MS. HEIDI WALLIS: Good morning.

DR. CYNTHIA POWELL: Hello.

MS. HEIDI WALLIS: I am.

DR. CYNTHIA POWELL: We can hear you. Thank you.

MS. HEIDI WALLIS: Okay, great. Thank you. Hi. My name is Heidi Wallis, and I serve as the Vice President for the Association for Creatine Deficiencies. I also work for the Utah Newborn Screening Program. But today I would like to speak to you as a parent and advocate for children affected by GAMT deficiency in regard to the Nomination Review Process of New Disorders.

In May of 2015, I provided comments in a meeting where GAMT deficiency had been nominated for addition to the RUSP. In that same meeting, just minutes before, discussing GAMT, the Committee had voted to change the rules for

considering any nomination for review. A key change was the addition of the requirement that a disorder could not be moved forward without a perspective find; 1) A baby identified at birth with the disorder through the process of a dried blood spot, tested alongside the general population. This small change resulted in GAMT not moving forward that day by one vote. Two years and four months later in New York in September of 2017, a beautiful and seemingly healthy baby girl was born. That baby's parents would go through an agonizing 19-month odyssey of begging doctors for answers as their daughter seemed to slip away before finally receiving their GAMT diagnosis this past spring of 2019.

GAMT is a degenerative disorder. The very best outcomes are only seen with children who receive treatment soon after birth. I know this firsthand, having a daughter diagnosed at 5, who is now 16 and intellectually disabled. She turned 16 this past Sunday, and she believed that she

would then be allowed to start driving a car. But that will never happen. She will never live independently. She recently underwent an invasive surgery to try to stop her recurrent seizures, which have lately resulted in broken bones, holes in drywall, et cetera as she is now adult size. The impact of this disease never ends for her or for our family.

On the other hand, my son is 7 and has been treated from birth. He has a normal IQ, enjoys playing sports, reading books, and playing with friends.

I believe that the baby born in New York in 2017 was directly affected by the May 2015 decision. New York is a very progressive state and they have voluntarily added GAMT to their panel this past fall. If GAMT had been added to the RUSP in 2015, there is a good chance New York would have moved even quicker to start screening. Just this one life would have been all worth it. Just that one vote we didn't get, all because one

perfective find hadn't happened yet.

I don't think babies were meant to be harmed when a rule is updated, but it's what did happen. I personally had to explain this to the mom from New York when she questioned RUSP and why her child had not been diagnosed at birth.

I tell you all of this to shed some light on the seriousness of the decisions made by this Committee, not to point fingers, but to ask you to please make a change. GAMT is indeed rare. Estimates typically range from 1 in a 125,000 to 1 in 500,000. For comparison, I looked at some of the primary conditions recommended on the RUSP, and a few ultra-rate disorders stood out that appear to be even rarer than GAMT. BKT deficiency is estimated to occur at a rate of 1 in a million. HMG is "very rare" with fewer than 100 cases reported worldwide. TFP deficiency is extremely rare with the number of cases unknown. But we keep screening for this -- these disorders. Why? Because this is not about profit. It's not about

how we can get the most bang for our buck when we screen. It's about the core purpose of newborn screening. If we screen for this, will we potentially save a life? And when the answer is yes, we screen for it, and we keep screening and screening even if it takes years to find a baby.

In closing, I'd like to say that requiring a disorder to be first found in a baby prospectively is an unachievable requirement from very rare disorders when like in the case of GAMT, states like Georgia reviewed the evidence supporting the treatment of the disorder is simple, safe, and effective, and they want to add the disorder to a pilot, but the disease is rare. There aren't big bucks backing the disorder, and no one is able to fund the pilot, while the pilot never happens.

Our organization can't fund enough pilots in enough states to quickly find that baby we need. I remind you we are very rare, and this means small pockets. We already know a baby has

been missed since this requirement has been added. I would ask that you please consider removing the requirement for one perspective find from the requirement for a disorder to be moved forward. If this can't be agreed upon to be removed, please consider perhaps rewording it with a clause to consider robust population studies conducted invalidating assays as also acceptable evidence of the efficacy of testing for the disorder. This would be much more of a realistic ask for very rare disorder groups to fund.

Thank you for this opportunity to speak.

DR. CYNTHIA POWELL: Thank you, Ms. Wallis. We do appreciate your comments.

Given the time, although we're a little bit early, we'll break for lunch. But, first Catharine has some announcements.

DR. CATHARINE RILEY: Hi. Thank you. Just -- this is just a general reminder as we break for lunch. The café is just across the pavilion, and then if you exit the building,

you'll need to go through security to get back in. We will have an escort by the main entrance for about 15 minutes before the lunch break ends if you need to come back in for the meeting. If you have other needs of leaving the building and coming back in, please let a HRSA staff member know so we can help you with that.

With that, we will begin the meeting again promptly at 12:30. Thank you.

[LUNCH]

DR. CYNTHIA POWELL: Okay. If everybody could take their seats so we can get started for the afternoon session. Welcome back, everyone. Before we get started, we need to do the afternoon roll call. So, we'll start with the Committee members. Mei Baker.

DR. MEI BAKER: Here.

DR. CYNTHIA POWELL: Susan Berry.

DR. SUSAN BERRY: Here.

DR. CYNTHIA POWELL: Kyle Brothers.

DR. KYLE BROTHERS: Here.

DR. CYNTHIA POWELL: Jane DeLuca.
DR. JANE DELUCA: Here.
DR. CYNTHIA POWELL: Carla Cuthbert.
DR. CARLA CUTHBERT: Here.
DR. CYNTHIA POWELL: Kellie Kelm.
DR. KELLIE KELM: Here.
DR. CYNTHIA POWELL: Michael Warren.
MS. JOAN SCOTT: Joan Scott is sitting in for Dr. Warren.
DR. CYNTHIA POWELL: Joan, okay. I'm here. Melissa Parisi.
DR. MELISSA PARISI: Here.
DR. CYNTHIA POWELL: Annamarie Saarinen
MS. ANNAMARIE SAARINEN: Here.
DR. CYNTHIA POWELL: Scott Shone.
DR. SCOTT SHONE: Here.
DR. CYNTHIA POWELL: Beth Tarini.
DR. BETH TARINI: Here.
DR. CYNTHIA POWELL: Catharine Riley.
DR. CATHARINE RILEY: Here.
DR. CYNTHIA POWELL: And for the

organizational reps, Robert Ostrander.

DR. ROBERT OSTRANDER: Here.

DR. CYNTHIA POWELL: Debra Freedenberg.

DR. DEBRA FREEDENBERG: Here.

DR. CYNTHIA POWELL: Mike Watson.

DR. MICHAEL WATSON: Here.

DR. CYNTHIA POWELL: Steven Ralston. Jed Miller.

DR. JED MILLER: Here.

DR. CYNTHIA POWELL: Susan Tanksley.

DR. SUSAN TANKSLEY: Here.

DR. CYNTHIA POWELL: Chris Kus. Jacqueline, I think, is not. Jennifer Kwon.

DR. JENNIFER KWON: Here.

DR. CYNTHIA POWELL: Theresa Hart.

MS. THERESA HART: Here.

DR. CYNTHIA POWELL: Natasha Bonhomme.

MS. NATASHA BONHOMME: Here.

DR. CYNTHIA POWELL: Siobhan Dolan.

DR. SIOBHAN DOLAN: Here.

DR. CYNTHIA POWELL: Amy Gaviglio.

MS. AMY GAVIGLIO: Here.

DR. CYNTHIA POWELL: Georgianne Arnold.

DR. GEORGIANNE ARNOLD: Here.

DR. CYNTHIA POWELL: Thank you. All right.

DR. CYNTHIA POWELL: So, this afternoon, we're going to be discussing the RUSP Conditions and Evidence Review Process, and what we've discussed thus far, what we plan on discussing today, and the next steps.

So, I wanted to go through a little bit about our approach to this and the timeline. As I said, today we'll be focusing on the systematic evidence-based review continuing our discussion on that, the principles of evidence review have evolved, and we need to determine whether changes need to be made. This review of the Committee's current evidence-based review process includes how evidence and information are gathered for the evidence review, the types of data and information included, how the evidence is graded and presented

to the Committee, and the appropriate method for determining the strength of evidence. It also includes a look at the decision matrix and the decision-making process. Our aim is to update the decision-making framework with the latest approaches for using evidence to successfully develop public health policies.

As you may remember from the April meeting, we're focusing our review on four main areas; the nomination, the systemic evidence-based review, the decision matrix, and the current conditions on the RUSP review.

In April, the Committee discussed case definitions at the start of the review process and the need to standardize terminology regarding primary and secondary targets and incidental findings pre-specifying outcomes and the use of intermediate outcomes such as biomarkers. The range of treatments that should be included; grading the evidence, identifying and synthesizing unpublished evidence and data. Today, we'll focus

our discussion on the systematic evidence-based review process, and in November, we'll discuss the decision matrix and the decision-making process. And in February of next year, we'll review the nomination process.

After the panel presents on the components of the current evidence review process, we'll have a discussion on the approaches to assess cost, implement population level modeling, and assess the impact on the public health system. We'll discuss a potential addition to the review process after the break, the assessment of values and the role this information could play in the decision-making process. As you listen to Dr. Kemper and his team present today, please be thinking about ways in which the methods used and data included in the evidence review can be modified to better inform the Committee's deliberations and decisions.

Okay. And Dr. Kemper and a panel of experts in the field will provide an overview of

the current Evidence Review Process, and I'd like to invite Dr. Kemper up to the podium.

DR. ALEX KEMPER: Thank you. Dr. Powell, thank you for setting the stage for what we're going to do this afternoon. And so, really what I'm going to do is tee up some of the decisions that we've made based on the last presentation that we had and talk about things that we need to do moving forward. But the real meat of the presentation during this part is going to come from first Dr. Lisa Prosser talking about modeling -- most it closer, okay. I'll try to be a little louder. How's that? It's amazing what happens when you speak into it. So, Dr. Lisa Prosser is going to kick things off by talking about the modeling, and then Jelili Ojodu is going to come and talk about the Public Health System Impact Assessment and where the opportunities are there. An important component of that is the cost analysis, which we, you know, certainly have discussed in the past, but Dr. Scott Grosse is

going to come up and present where things stand and also some options with that moving forward. So, in this first part of the presentation, I'm just going to tee things up and, of course, I'd be remiss if I didn't thank K.K. Lam for all the work that she does on behalf of this.

So, our overall project objective is to look at the evidence-based process leading up to the addition of a condition to the RUSP or at least consideration for addition to the RUSP, and identify ways to improve the process.

So, as I talked before, I'm just going to give an overview or the process reason for updating things. I'm going to recap decisions that we've been made -- that have been made and then we're going to do this deep dive into the modeling and the Public Health System Impact Assessment, of which cost is an important component.

So, just to remind you, back in February of 2019, we had an Expert Advisory Panel, which

considered the full range beginning from nomination through the evidence review process, the decision making, and as part of that, there was a consideration -- there was a discussion of consideration of how to review conditions that are already on the RUSP. Again, we're not going to be talking about that part today. Our goal is to have a summary report based on all that by March. And we're having, at these meetings a series of facilitated discussions. So, in the March 2019 meeting, we provided an overview of what the Expert Advisory Panel said and then in the April meeting -- the meeting we had just previous to this -- we talked about the systematic evidence review process. Today, we're going to be talking about decision modeling and the Public Health System Impact Assessment, cost assessment, and then after potentially a break that is much needed, we will talk about values. Then in November, we're going to talk about the decision matrix, and then that will lead us into February,

where we can talk about review of the conditions already on the RUSP as well as the nomination process.

So, I present this just so you have a good sense of where the train is going.

So, as everybody in this room listening to the webinar understands the evidence-based reviews are enshrined within the Newborn Screening Saves Lives Reauthorization Act, and included in that is the requirement that the Advisory Committee shall evaluated the public health impact including cost of expanding newborn screening, and then I'll also remind everyone there is this 9-month process from when a condition is handed off to when a vote first comes up. Now, I say 9 months, but it's actually a little bit less than 9 months based on the cadence of when the meetings are and when things get handed off. So, in reality, it's probably closer to like 7 months than 9 months, but given the language in the law, I have 9 months written here.

So, the -- the three components include the evaluation of evidence of clinical effectiveness and net benefit, which again we talked about extensively, the public health impact assessment, which gives a population-level perspective, and again Dr. Prosser is going to talk about this in her modeling, and then there's the public health impact assessment side of things which looks at the newborn screening program side of things in terms of feasibility, readiness, and also the cost of this program expanding screening, and again Scott Grosse is going to talk about what we mean by this issue of cost and what we can get to.

So, I share this slide just to give you a sense of the timing of the various components broken into the three-month parts, and again, you know, it's sort of optimistically listed as nine months, but in reality it's not. The key takeaway from this slide is there are certain components that are dependent on other components. So, for

example, the modeling that Dr. Prosser is going to talk about depends upon having a good understanding of the evidence that's out there to be able to build the model. So, not each component of the process can begin at the same moment because of this dependency.

This is just another way of breaking out the timing and the point to make here is that we have things set up so that there is an interim Advisory Committee meeting where we can present what we have learned so far, and that gives us an opportunity beyond just working with the liaisons from the Advisory Committee who are involved in the review process, but the whole group to see if what we are doing meets the needs of the upcoming vote or whether or not we need to modify anything.

So, I'm going to go through and just talk about the decisions made around the Systematic Evidence Review Process, and then I'm going to be handing off, like I talked about before. I think this presentation is going to work best if at the

end of these major sections that are going to be presented, if there are clarifying questions, I think we ought to put them up. But in terms of the more detailed considerations, because everything sort of depends upon each other, I think it makes sense to wait until all the component presentations are done. Does that make sense to you all? Okay, good.

So, in terms of recap of the recommendations that we've gotten from the case definition, we got good advice about how to be more streamlined and focused on that. From the health outcomes that we look in the evidence review process, we have developed over time the standard prespecified outcomes as well as condition-specific outcomes that we'll be able to identify earlier on in the process. We will be more clear about the issues of time horizons for outcomes. And then, we will -- we've also developed ways to be more clear about the key treatments that we need to look at, which, you

know, can be pharmaceutical treatments or non-pharmaceutical treatments. They can be specific for the condition or could be nonspecific, and by that I mean more sort of broad, supportive interventions. We can look across all those different types of interventions. But, the important thing is just making sure that we identify them early enough in the process so that we can evaluate them. We have a quality -- quality appraisal process that's based on looking at each individual question in the evidence review as well as -- I mean looking at each article as well as across the -- the particular key question, and that was based on grade, which we talked about before. And then, we have more clear ways of handling the gray literature. Again, this are all things that we talked about at the last meeting.

So, with that by background, and again, I just really wanted to make sure that everyone understood what has come before as we transition to talk about new issues in the evidence review

process. I'm going to ask Lisa Prosser to come up here, and as she does, if anybody has any clarifying questions on our approach in terms of what things we're looking at or on the evidence review process, otherwise we can dig into it more later. I'm going to go really quickly since I don't see any hands up and I've learned the art of stepping away before they do come up.

DR. LISA PROSSER: All right. Great, thanks Alex. Terrific. Properly named here, right, identifiable grade. Thanks very much. Well, thanks everyone for an opportunity to talk about our population -- population-level estimates here today. So, can everybody hear me okay?

So, I'm going to start before I jump into the slides just by giving a little bit of a background as to why we're doing decision analytic modeling as part of the evidence review process. When you think about similar processes for other types of evidence review in other areas of public health or evaluating health interventions, that it

is typically a more traditional evidence review process where we evaluate what evidence is out there, sometimes including the gray literature, and then we'll summarize that and report that to the Advisory Committee.

In 2011, we took a pause here -- this Committee and the Evidence Review Group -- after there had been a number of conditions that had not moved forward due to a lack of sufficient evidence. So, there was a determination made that it wasn't beneficial to potentially screen for these conditions, but the determination was that there was insufficient evidence to decide one way or the other. So, at that point, we took a pause and evaluated other methodologies that we could incorporate into the evidence review process to make the best advantage of the evidence that we did have available for these very rare conditions.

What we decided to do was incorporate decision analytic modeling or decision modeling or simulation modeling -- I'll use those terms

interchangeably during this presentation -- which is a systematic approach to decision making under conditions of uncertainty, and I'll give an example in a few slides of how we've used that in evaluating past conditions.

More broadly across the evaluation spectrum, it can be used to simulate randomized control trials, for example, for drugs that have not been tested head-to-head, but we'd like to simulate that head-to-head trial for new interventions to project estimates beyond the trial time frame and that is certainly something that we've done here to compare treatment protocols also, not directly compared in head-to-head trial, but also to evaluate in creating assumptions of how those interventions might perform in populations beyond which the clinical trial or the study data are available for, which is another option that we've used here.

Overall, our goal when using decision modeling is to identify which alternative or which

strategy, and here we're comparing population-level screening compared to no screening or clinical identification, which one is expected to yield the most public health benefit.

We can also use decision modeling, and we've done that here, to characterize uncertainties in the data, understanding the long-term clinical and economic outcomes and what is the range of uncertainty around those estimates, as well as where are the key data gaps. So, when we're conducting the analysis as we vary those parameter inputs, we have many uncertainties, and the level of evidence that's driving those assumptions, and we can identify where, looking down the road if we wanted to invest in terms of additional research data collection, that those would likely yield the most benefit in terms of narrowing those -- those intervals.

And so, how we've applied it here to the condition reviews is narrowly to estimate the range of health outcomes expected for universal

newborn screening for a specific condition compared to clinical detection, and based on a very specific case definition that's the objective of newborn screening, and so we'll talk about that in a couple of slides. And so, we project estimates based on a US birth cohort of 4 million children, the projected number of cases of the condition detected at birth through newborn screening compared to clinical identification, as well as projected health outcomes, so deaths averted, cases of ventilator dependence avoided, other potential health benefits, if we have enough data to do that.

So, just a brief overview of our current approach is that for each of the conditions since 2011 that have been evaluated, we've developed a simulation model. This has been done collaboratively with a technical expert panel that represents national experts in the clinical condition, and we also typically have liaison members from the Advisory Committee who are part

of the Evidence Review Group, and we develop a structure for the model, develop input parameters, identify what the key outcomes are, and often that's an iterative process that revises the analytic model as well as the assumptions along the way. Typically, we, as with any type of model, we start with a more complex model and then as we evaluate the evidence, we typically prune that to reflect the evidence that we have that's available.

So, I'm going to give an example of using SMA of how we apply this to evaluate the target population, specifically focusing on one type of SMA, the intervention, so looking at newborn screening and applying the data that we have to presymptomatic infants where we had primarily data on the treatment of symptomatic infants. The time frame in this case was only one year, and we're using this as an example because it really illustrates some of the questions that came up during the Expert Advisory Panel that we held in

March of this year, and the key health endpoints here were mortality and ventilator dependence.

And if you think about simulation modeling more broadly, typically many of the models that we have are much more complex than this, but here, the intent is really to keep the models as simple as possible so that the assumptions are easily understood that this -- this analysis can be completed within the time frame that's required. One of the areas that would be very advantageous, we've talked about it on this committee before and Scott Grosse will be talking about in a little bit, is the addition of cost and how we might potentially be able to incorporate that into this analysis.

So, this slide here just shows an example of the -- of the simulation model for SMA. As you can see, we've defined all the health states. I will not go through this in detail, but just to state that as we build this model, we reflect the structure back working with the Technical Expert

Panel. We typically meet with them several times throughout the process. During that interim meeting with the Advisory Committee, we'll present the preliminary model. Here you can see all the health states that are involved. We define the health states, we define the outcomes, and then every single arrow on this model represents a probability that must be estimated. And so, sometimes we have so little data that we're actually varying that probability potentially all the way from zero to 1. Typically, we have some evidence that we can narrow that down, but it's important to keep in mind as we build these models, we're applying probabilities to each one of those arrows that's represented in the model.

So, this slide shows the results from that specific example of SMA. So, comparing in the middle column, again, this is assuming a healthy annual newborn cohort of 4 million, not at higher risk of SMA. The target for screening that was agreed for in terms of the analysis was Type I

SMA, understanding that there are likely to be benefits for other types of SMA, but that was not the focus of the evidence review or the simulation model that we were focused on the specific category of the disease that was likely to benefit the most from newborn screening.

And so here, we're able to project estimates both for the number of newborns that would be identified in total in newborn screening compared with clinical identification. I think what's interesting to note for SMA is that for newborn screening clinical identification, the assumption was that the number of newborns that is identified would be the same. We often observe an increase in detection under newborn screening compared with clinical identification, and typically that's something we would incorporate into the modeling and can give us an estimate of what the range of those benefits are likely to be, depending on how much that varies across conditions.

I'm not going to go through these in detail, but just to note that in parentheses, that represents the range of results -- the uncertainty around these results for the condition. In terms of longer-term health outcomes for SMA, we only had one-year outcomes that we were able to model, and so there were -- we modeled a substantial model of deaths averted as well as ventilator-dependent cases that were averted. I think in the context of the conversation today, important to note that this is the shortest time frame that we modeled in any of the conditions that we've modeled so far. For most of the conditions we've modeled, we've been able to model several years of data, for some up to age 8, and for one condition, through age 15.

So, just in terms of the summary, so again the goal of the decision analysis is to project population-level health outcomes and also to identify what that range is given the best available evidence that we have. And so here

we're able to identify the number of cases as well as the number of Type I cases, and identifying that there would be both reduced deaths in cases of ventilator dependence for newborn screening compared with clinical identification, and again noting that there are additional benefits, and this can be part of the discussion but was not part of our specific modeling exercise.

Important to note and one of the areas of conversation that came up repeatedly during the modeling of SMA was that we only had 52 weeks of treatment effectiveness data as well as for the new natural history. So, trying to estimate what the long-term outcomes would be for newborns that were screened and then treated pre-symptomatically, we had overall very little data in terms of modeling those that combined the clinical trials represented on not quite 200 patients, and again 52 weeks was the longest time frame that we had within those data sets. And so, just to understand that there's a lot of

uncertainty around long-term outcomes for that and compared to other conditions, it's fair to say it seemed as if we were kind of on the edge of having enough evidence to model or not. And so, that was a discussion that we had during the EAP meeting in March is considering the availability and type of evidence on the condition, can we do this before the evidence review to make a determination as to whether there is sufficient information to complete all of the parts of the evidence review including the population-level modeling, or if it might be necessary to go forward with the evidence review but insufficient evidence for the -- for the population-level estimates. And where we came out -- and just to note, I think, you know, Alex covered this in the last meeting talking about a systematic method for including assessing unpublished or expert derived evidence as part of the overall process.

So, I mean, in the context of the evidence review process here that we -- we are

always working with rare disorders. I mean, that is the definition of what we're doing here, and the evidence base will always reflect that. We'll have small studies, we'll have single-arm studies, and that's why we're using decision modeling as an approach to evidence synthesis to be able to really make the best advantage of the data that we do have, and we do need to rely on the gray literature and expert input for modeling assumptions.

But what has been observed is over the last few years that more recently nominated conditions are being nominated for the RUSP earlier in that pathway of, you know, where the treatment is in terms of the level of evidence, so that there is a lower evidence base at the time of the nomination, and a recognition that modeling may be feasible for some nominated conditions depending how soon that happens.

So, we had an expanded discussion about whether we could think about a criteria for

determining at the time of the nomination if it was -- if there would be sufficient evidence to conduct modeling or not, and where we came out was that it's -- it would be difficult to define a specific set of criteria because of the variability of the types of evidence that we use in this process and because for every condition, it's going to be a different combination of types of studies, sample sizes, et cetera. But that what we would recommend going forward is just to ensure, as we typically do -- we strive to do, is that there's transparency during the model development, that we have an open conversation about summary tables of the studies that are being used in the model, ongoing active communication with the Advisory Committee. If, during the review process, it turns out there may not be enough evidence, that we would have that conversation that we may need to forego modeling for some of the condition review processes and to discuss what that means for the Committee process.

So, I'm going to pause there. I'm happy to take clarifying questions at this point, and then I'll turn it over to Jelili.

MR. JELILI OJUDU: Good afternoon, everyone. Let's see here. So, in continuing on with the conversation here as noted a number of times today, as part of the Newborn Screening Saves Lives Act or the Reauthorization of the Newborn Screening Saves Lives Act, there was a particular line that included the evaluation of the Public Health System Impact of all of the new conditions that are added to the Recommended Uniform Screening Panel, and that's where our lives started to change a little bit.

The purpose of the Public Health System Impact ideally is to get a sense from the newborn screening committee and stakeholders including advocacy groups about the difficulties -- well, let me take that back -- the opportunities, challenges, and other kinds of implementation barriers as to what states may be facing when

they're adding new conditions to their own state panels. Describing the overall feasibility and readiness of adding a new condition, which I'll talk about in a little bit, and then describing the cost and, you know, no better person to talk about cost than Dr. Grosse. So, I'll talk briefly about that, and he has a number of slides that he's going to highlight on cost prospectively, retrospectively, and some of the things that we're thinking about in the future.

So, how do we do all of the things that we do related to the Public Health System Impact as part of the Evidence Review Workgroup activities? It's first gathering a good amount of information. Now, let's step back for a minute. Most of the states that are thinking about adding a new condition -- in this case, conditions that have been nominated to be added to the RUSP -- are not actually screening for those conditions. And so, they don't have enough information regarding testing, everything related to the implementation,

treatment. So, in essence, we developed a number of informational fact sheets that we gather working with a number of states, and there are a few states that will normally start screening for these conditions whether in pilot stage or actually mandating the screening for one of these conditions before it's nominated to the RUSP. Gather that information and work with a number of folks to be able to provide that to state newborn screening programs in the form of webinars -- informational webinars that contain, among other things, the cost of testing, testing modalities and methodologies, how much it cost to be able to start the implementation kind of activities, whether it's the laboratory, reagents, short-term follow-up. We don’t get too much into the treatment aspect; however, we do note exactly, you know, some of the -- the path or, you know, some of the activities related to in fact what the folks at ACMG then put into their own factsheets for those new conditions as they come up.

I'm going to take you another step backwards. Dr. Kemper briefly mentioned that although we have a stipulated mandate to be able to do all of this great work in nine months, and he said it really is seven months, from our perspective, it's actually less than that, and I'll highlight some of the reasons why, whether it's administrative or, you know, how we are able to gather all this information and informing our members, state newborn screening programs, and making sure that they can then respond back in the surveys that they provide to us information on -- hypothetical information on how they would screen or bring on a new condition into their state panels.

When we survey states or anytime I say survey states, it's 53 newborn screening programs, so 53 states, Guam, Puerto Rico, and the District of Columbia, we would administer and this -- it takes a village to do these kinds of things -- an online survey and distribute it to all of the

state newborn screening programs to be able to get a sense of how feasible it is to be able to bring on a new condition. The hope -- and we stress this a number of times -- is that the newborn screening program directors -- it could be at a laboratory level or program level, at follow-up, newborn screening lead -- distributes the survey extensively throughout their own state newborn screening system, and I'll talk a little bit about that in a minute as well. And then, we also do follow-ups, so these surveys normally take -- we survey our members to death, and sorry about that, this is important, and we try to emphasize why as part of ACHDNC consideration in adding a new condition, why members should be providing information back to us.

It normally takes about four weeks -- four to six weeks to be able to get 40 to 60 percent of the states to respond to the survey. It takes another two to three weeks to follow up calling, saying hello, please complete the survey

in question to state newborn screening programs, and then for the remaining states that haven't either responded to us, we find other means to be able to get them to do -- complete that survey. And as part of the overall activities, analyze the survey and final report. This is to all newborn screening programs, as I noted.

We also do an in-depth overview of follow-up activities to newborn screening programs, for lack of a better word, early adopters, those one, two, or three states that brought on the condition, whether in pilot stage or they're almost at the point of bringing the condition to their state newborn screening panel or have a mandate to screen for those conditions, you know, and extensive in-depth kind of overview about their processes. This helps a great deal to better understand their own newborn screening system, which, I think, is very helpful to a number of states.

I should note though that for the most

part, although the information that we gather from states that are early adopters to bring on a new condition is helpful, it is not necessarily transferable to every state newborn screening program, because there are a number of nuances that make each state different. We anonymously provide this information to you all and make sure that folks know that we have their best interest in hand in sharing and responding to, you know, the needs of the Evidence Review Panel here.

It's been mentioned quite a bit today about the meeting that occurred I think in February of this, the Expert Advisory Panel, and they -- we met here in HRSA, a group of folks, and they came up with a number of issues or things that we should consider as part of our Public Health System Impact as we move forward, and these are observations of Public Health System Impact that we've done for at least the last four conditions, Pompe and PSI, X-ALD, and SMA. I get up here, I present the results of the survey, and

I almost always tell you that it will take about a year to three years for these conditions to be added to state newborn screening programs. But, in fact, that's -- at least from this group's perspective -- it wasn't informative, and there is good reason to actually understand that. The understanding of the burden of sub-specialties when it comes to either true positives or the false positives is something that I think we need to do a better job of either pulling out of our survey or asking from our state public health programs when they are providing information back to us, the need to better make sure that states are pushing this information out to all of the folks in their newborn screening systems. And again, you know, some states may not have actually reached out to some pertinent sub-specialty that will be involved in their newborn screening system when these conditions are being considered. And so, you know, it's something to consider for sure.

The long-term aspects -- long-term

follow-up aspects of some of the things that we do are not known certainly by the time we're creating this informational packet, and certainly for many years afterwards, it's something that we are still learning.

And finally -- and this was just a few of the things that were raised by the evidence -- by the Expert Advisory Panel -- and it's something that we've heard from a number of states, what is the -- how is the Public Health Impact -- System Impact information either used to consider or make that final decision on adding a condition, and what is that impact of that public health system information that we are providing? I think there are a number of states that from time to time ask us that question, and I think it's something that we would certainly need to do a better job of translating to them and also getting guidance from you all Committee members.

So, I noted a few times the hypothetical aspect of a survey and asking a question, what

will it take or how long will it take or what do you need to be able to add a new condition to your panel. This assumes that a state newborn screening program has the authority to actually do or screen babies, which is something that is -- there are a number of things that have to happen before they get that authority to screen, and then this question asked, you know, after all of that, what are those hypothetical feasibility and readiness kinds of aspects including funding, which almost always is going to be a barrier. But, you know, the legislative processes, I think there are -- the majority of states actually have to have a legislative mandate to be able to screen for a condition, and without that, the questions that we are asking, you know, need to be either a little bit more clear or we have to have -- we have to at least go in with this -- knowing this limitation and expecting or not expecting too much when it comes to the final results and how that shapes our thinking for the next one, three, or

many years that it will takes states to be able to add a condition.

I'm not going to talk too much about OMB at this point, other than the fact that when you're surveying a number of states, we do have a process in play where we are -- we've been able to have a broad survey -- electronic survey that we send out to state newborn screening programs for any one of the conditions that are added to the RUSP. To change anything in a survey at that level takes a longer time than -- than the nine months that we are expected to come back with results from the Public Health Systems Impact. So, you know, think about the -- the different conditions and how each of them have unique characteristics when it comes to state newborn screening programs. Our survey, while we have worked on improving it, is somewhat limited in the kind of information that we can get back. Revision is underway and already completed.

So, I don't want to sound all doom and

gloom here. This, in fact, survey does help to inform you all, and I do have one slide that actually shows a good amount of information that's been collected over the last several years. As part of NewSTEPs, we collect information related to states readiness to be able to implement a new condition, and we are looking for -- at this point, we are in the process of finding ways to be able to incorporate things that we collect as part of NewSTEPs related to this readiness tool ideally to be part of the, you know, the Public Health System Impact Survey, and being that states are already providing us with this information for conditions that are being either considered or added to the RUSP. We have made changes to the survey in question including the interview questions over the last year and a half that I think will help improve and enhance what we currently do. And again, it's encouraging -- we want state screening programs to be able to make sure that they share this -- the Public Health

System Impact Survey with all of the stakeholders in their newborn screening program.

There's a lot of information here. I'm not sure it's -- the only thing we're highlighting here is if you can see the left-hand side, at least that -- that side on the left-hand side. That's our -- just the snapshot of our -- the beginning of our survey that expired in 2018 and again, it's, you know, how long would it take to achieve the following assuming that condition "x" is added to your state newborn screening panel if allocations or if funds were available. That "if" makes a big difference there. One year or less, one to three years, or three years or more. Fast forward to what we have right now, that is going through the system, and I think hopefully will be approved. We've broken that timeline down into a little bit more that I think we'll be able to better understand. In fact, you know, if it takes a little bit less than a year, and the timeline is in months there. That will be hopefully more

informative as we move forward.

So, potential recommendations and solutions. I think we have worked hard to be able to describe two state newborn screening programs and the process of, in fact, obtaining the legislative approval. I think we need to do more here, but -- and then, as it relates to the condition nomination team, it probably will be helpful to be able to get some kind of long-term strategies in helping us and you all better understand how to move forward, especially noting some of the limitations that I mentioned earlier.

So, these are the last four conditions that have been added to the Recommended Uniform Screening Panel, the dates that they were nominated to or they were nominated to the -- to be added, the decision matrix number that followed after the decision was made, the date that the condition was added. I talked earlier about reaching out to state newborn screening programs to be able to get a sense of how population

screening works when those early adopters are screening.

At the time of screening -- at the time of bringing on a new condition for any one of these three conditions, as you can see, the most number of states that were screening that condition, whether as a pilot or mandate was three. So, the majority of states, 95 percent or more, weren't.

Let's fast forward a year to three years and see how many states were screening for those conditions. Most, again, is about nine of the fifty-three newborn screening programs, and in fact, it's the last condition that's been added to the RUSP incidentally. Three years out, there are about eighteen states that are screening for the majority of those conditions -- the majority of the three -- of the four conditions that have been added to the RUSP, or wait, and then years and then how many conditions are screened -- how many states are screening today. Oh, today is August

1st, yes. Approximately twenty states are screening for these conditions as it relates to their state newborn screening programs today.

Now, there are a number of caveats here. I'm not sure if we will be able to have these many states screen for these conditions if it wasn't for implementation funding from a number of feds around the table, whether it's NIH, CDC, or indirectly through HRSA. A majority of the states that are screening for any one of these four conditions actually got funds with IDIQ funds from NIH or implementation money to be able to support their screening there. Just something to think about. Then, the uniqueness of every condition that has been added to the RUSP.

I see that part of my slide set was taken out there, but the last column talked briefly about the -- the vote for each condition as it relates to the -- the ACHDNC recommendation and the Committee's vote, and there is a variability in the number of -- in votes. I don't think we

have had a unanimous vote for any one of the conditions that have been added to the RUSP -- at least not yet -- and as we move forward with adding new conditions, keeping in mind that this is what we have gotten through at least for the last conditions that have been added. I think it will be very important to be able to at least set the stage and understand the challenges and opportunities that we have facing state newborn screening programs when it comes to adding conditions and how long it may take them to do so.

So, with that, I'm going to have Scott come and talk a little bit about cost.

DR. SCOTT GROSSE: Thank you, Jelili. Thank you. I'm going to start by talking about the processes used for the SMA cost assessment. Previous conditions used different approaches. There was a Cost Assessment Workgroup that met and came up with the recommendations for a new approach. That tool that was developed asks for states that have started screening or about to

screen one of the proposed conditions to come up with costs for separate components; the staff time, equipment, reagents and other disposables, and facility overhead and space, and then the information from those states that are able and willing to share is then pulled and reported in aggregated form. The other costs can be reported, but the focus is on the direct costs of screening and the confirmatory testing.

So, SMA was the first condition for which that new framework was used. The two states, New York and Wisconsin, provided information. Both states were multiplexing SMA with the SCID molecular assay, and the overall cost estimate was between 10 cents and $1 per infant. The report did not provide the breakdown on that cost; however, all the -- or almost all the disposable -- the reagents and other disposables, the assumption was there would be no additional labor for this screening time or additional equipment.

So, challenges with this whole process of

trying to estimate costs. The estimates are projected costs because the states that are giving these cost estimates typically have not yet started implementing screening. They are projecting what they expect the costs to be. The estimates may differ that when states actually are implementing and need to calculate how much they're going to have to raise the fee when they implement the screening, there may be other cost components that need to be considered, administrative costs in particular, as well as the short-term follow-up costs. Only a limited number of programs, the early adopters, that are the pioneers may have very different infrastructure and experience in adding costs. Other states may have very different cost experiences. There are assumptions that are made about equipment costs, prorating the equipment cost. You need to know what is the useful life of the machine? How many years it is -- three years or ten years. Do you include the cost of maintenance contract, what

about utilities? It's very difficult to ensure that the estimates that are being provided are standardized, let alone generalizable to different states.

There's high variability across states and across screening laboratories in terms of the numbers of tests being performed, and it's really the laboratory cost is a function not of the number of births in the states, it's the function of how many specimens are being processed by the laboratory, and that varies also with one specimen or two specimens per states. There are contact labs. Do states purchase the equipment, or do they rent the equipment along with the reagents? There's a lack of -- there's high variability. It's not a limitation, it's just a feature.

The costs differ depending upon whether a condition is multiplexed or if it's a standalone test. May states cannot provide us information, because they are actually contracting. The information may be proprietary.

And finally, there's a short -- may be a short shelf life of the cost estimates to the extent there is a change in the technology. If a standalone test is replaced by multiplexing, the cost may go down substantially from what it was originally estimated.

Then, there's a broader question like Jelili asked about the PHSI -- how are the estimates actually being used by the Committee? To date, all the estimates, all the conditions that have been approved have had cost estimates of less than $10 per infant. Would -- it appears that those costs have not factored into the decisions. Would a higher-cost test -- if there was a condition that the screening test cost $20 per infant, would that move the needle? Would that affect the decision by the Committee? I don't think the Committee has addressed that decision. Does the Committee actually need a numerical cost estimate to make its decisions, or would a qualitative estimate be sufficient? Would

it be sufficient to say we think it's less than $10 per infant? How have the cost estimates been used by states? Have states found those cost estimates that have been generated through this process useful? What has their experience been? I think it would be helpful to get some feedback from the states.

In retrospect, we can look back at the conditions like SMA. We now have at least one other state that has implemented, and they've confirmed that about $1 per infant is a reasonable cost estimate, but others think the cost may be substantially higher. It very well may be higher if it's a standalone test -- it would be. I found a quote of someone who suggested the cost of SMA might be as much as $10 per infant. Who knows?

Issues that were raised by the Expert Advisory Panel, they say the cost estimates need to be both internally valid and generalizable across states. That would be wonderful if we could provide cost estimates as part of this

process. But within the time constraint and the lack of states actually doing the screening, that's not going to happen. They ask which costs were most important, how should they be measured, and how should that information be communicated. Well, is it the cost components that are important or the ones that are feasible to estimate? There may not be much overlap between the two. Not all that's important can be measured. So, we can give you the data that we can collect and address the limitations saying that there are costs -- other costs that should be considered.

Follow-up costs should be included. Yes, we agree. Follow-up costs, short-term follow-up staff, monitoring, that should all be included. The cost assessments typically do not account for the effort of the leadership of the program in the health department -- the director's time is a valuable and scarce commodity. Quality control, contractual issues with upgrading equipment, and also how does the cost differ depending upon the

level of funding -- external funding that may be available.

Potential solutions and recommendations moving forward -- it would be great to have a consistently frame cost assessment tool, even more than what we had previously. So, we just need to refine that. But more importantly, we need to have some kind of an incentive for the state programs to provide that information. And so, one possibility that we've discussed is that all -- moving forward in the future -- that pilot studies that are federally funded might be -- the recipients might be asked to collect and report that cost information using common data elements to make the estimates more comparable. That retrospectively, someone might collect cost data from the programs that have already implemented screening for new disorders, and those data then could be analyzed to come up with a cost function on how costs vary based on characteristics such as the number of specimens per infant, the number of

births per state, so we could actually come up with a better predictive model in the future of how costs might vary across states based on those different characteristics.

It has also been suggested by some that the cost assessment be broadened. The legislative mandate did not specify how costs were to be estimated. The decision was made several years ago to focus on the short-term costs to the newborn screening programs due in large part to the time constraint of expectably seven months, because realistically to do a more complete cost assessment would take a minimum of a year and a half. It's not going to happen within this time frame, and that doesn't mean that it can't be done in the future to estimate both broader cost and cost effectiveness, but that would have to be done in a different context. It could be done potentially as part of a post-RUSP review if sufficient funding were available to allocate to that, and that depends both on broader budgets and

priorities for allocating available funding. That's it. Thank you.

So, who's going to moderate the discussion, Alex?

MR. ALEX KEMPER: What I'd like to do, I think that [inaudible] I was going to invite Jelili and Lisa to come up as well, because I think that each of us oversee a discrete component of the -- of the Evidence Review Process, and I think it makes most sense for us to open things up. So, you know, I'd like to hear what people have to say about each of these three components or the process overall.

So, you've heard recommendations about ways to adjust the modeling, adjust the survey work that we're doing, and adjust the cost, and although, you know, we're always welcome to advise and open to answering questions, we wanted to take this time to open it up to the floor.

DR. CYNTHIA POWELL: Thank you. Thank you, Alex, and thank you -- all of you for your

presentations. So, we're going to first open it up to the Committee members and then followed by the organizational representatives. So, if the operator can please open the lines for Committee members and organizational representatives on the conference line, and just a reminder again, when speaking, please give your first and last names to ensure proper recording. And first, Joan has a question.

MS. JOAN SCOTT: Joan Scott, HRSA. Thank you so very much. This was an excellent, I think, overview of all of the complexity around components of the -- of the Evidence Review Process. My question, Lisa, was for you. You had started your presentation around some of the decision that went into why we started to do modeling because of the rarity of some of these cases, and then in your last slide, though, you indicate that modeling may not be feasible for some of the nominated conditions. So, can you say more about what those circumstances would be and

how that may affect the information that the Committee would have available to make decisions?

DR. LISA PROSSER: Yeah. And I think, you know, that's a great question and exactly where this discussion should be that, you know, there could be cases were you -- we could imagine, but we haven't seen this yet, that the condition comes up for nomination very quickly after treatment has been approved, and we may have even less than a full year of data available for modeling that condition. And so, what, you know, we have discussed, you know, is there a time frame or a sample size that we could create some parameters with it, you know, beyond which it would not be possible to model, and it didn't seem like that was the appropriate path because again, this is modeling. So, we're making the best use of the available evidence, and I think, you know, when I'm teaching modeling, that I often say, you know, well it's easiest and the most fun to model in the absence of data, and clearly we don't want

to model in the absence of data for this application, but, I mean, there are circumstances in which we can model with very little data. What we'll see is that we'll be much wider ranges around those estimates. I do think -- but we do think that there could be some situations in which we start to create the model and there is -- there really is not sufficient evidence to parameterize all of those branches that we showed on -- on the model, the example that I showed there. And if that's the case, we would want to have the opportunity to come back to the Committee to discuss that, and then I think it would be a case-by-case decision or I think this would be a discussion as to whether a nomination can proceed if it's not feasible to do the decision modeling, if that is an essential part of the condition review, or if it can move forward and be evaluated fully, you know, with the evidence review -- the population health impact, but without the decision modeling projections, because I do think that's a

possible scenario going forward.

MS. JOAN SCOTT: So, from that, the way I think of this, then, you know, the less data or the shorter time intervals we've got data, the more uncertainty you're putting into your decision, and so do we get to a point where the data is so uncertain about the impact that that is -- that it would be difficult for the Committee to move forward on it?

DR. LISA PROSSER: That's right, and that would be kind of the implication of not being able to complete the decision modeling task, yeah.

DR. CYNTHIA POWELL: Scott Shone.

DR. SCOTT SHONE: Hello. Scott Shone. I'll state my name even thought it was just said for me. So, I have a -- I have a couple different questions, but I'll just start on one, and then if I come back at the end after the rest of the Committee goes, I'd appreciate it. So, I want to preface it be saying that throughout the presentations and especially with Jelili and

Scott, I get the sense that we are -- that we keep giving lip service to newborn screening as a system, but a lot of the focus of the impact assessment and cost -- we're just program. We're just lab and maybe a smidge of follow-up. To suggest that implementing a disorder will only cost $3 a sample is patently ridiculous and so, I think that we have to either decide we're focusing on newborn screening as a system and think of system wide solutions and assessments and understanding or -- or stop kidding ourselves. Because I think that the huge gains we had with timeliness was because we began to engage everybody. We engaged the hospitals, we engaged couriers, we engaged informatics, and brought together a broader solution to make sure samples were getting screened and reported out as quickly as possible. We've got a lot more work to do on that front, but still, that was why we -- we had gains here. You know, Jelili, I'm just going to focus my question to you first, and Scott, I'd

love to come back later and talk about cost. But, you know, you started out by saying the one to three years is what you have -- you have stood in front of the Committee for the last several disorders and said one to three years, and you acknowledge that it -- it is not reality, and that your slide hammered that home. You know, the disorders are progressing at very different paces. Dr. Kellar-Guenther's presentation to us at the last meeting really dove into the nitty gritty of why that's happening, and I think that perhaps we need to use that information, and can you comment on can we combine what you're getting out of the readiness tool as well as the structure of the impact assessment? Because it doesn't seem like asking the same question every time is getting us anywhere. There are different things that arise. You know, SMA might be moving faster because the treatment is being viewed as transformative as opposed to the other disorders where there might not be will within the state to do ALD.

So, can we incorporate some of those lessons into this as opposed to just changing the timeline for how long a state might think, you know, it takes to implement if we don't assume there's legislative support and budget?

DR. ALEX KEMPER: So, I just want to preface before Jelili answers your particular question about the data gathering process is to just remind you and others that for each of these individual components, it's one data point that has to be considered within the whole milieu. I mean, there's no simple question, and that's why we have the Advisory Committee in the first place, to use your -- your experience and your knowledge of newborn screening to evaluate these discrete data points that you have. And I just want to be clear about separating the information that we can provide based on either published evidence or surveys with states and that kind of thing versus how that information is subsequently used. Because that's where sort of the dividing line is

between what our group can do and what the Advisory Committee can do, and I just want to make sure that -- that we're clear about what that line is. And that's why I just jumped in front of Jelili, not because he's -- he's going to give you a very thoughtful answer about what's available and the readiness tool and all that, and I just want to be -- I just want to be very clear about what I see as a decision versus data-gathering point. But I -- and I agree with all the points you just made, Scott.

MR. JELILI OJODU: So, thanks, Scott. Let's see, where do I begin? The idea, in fact, is to be able to make some changes or ideally bring in some of the information that we collect as part of the readiness tool. As you know, readiness tool information are the information that we gather are from conditions that have already been added to the RUSP. So, I think if we can combine partly some of that information that we collect with the survey or the revised survey,

the Public Health System Impact Survey, I think we may be able to get a little bit more refined answers.

But to your initial question, I'm not -- the evidence speaks for itself from when the conditions have been added, what we got from the results of the survey, and what is actually happening in state newborn screening programs. I wanted to emphasize a little bit more about, you know, and in fact some external sources that probably made it so that we are where we are for the number of conditions that we're screening for, and if it wasn't for again some of those funding streams afterwards, you know, the numbers would be even lower. So, I'll stop there.

DR. SCOTT SHONE: This is Scott Shone. Just real quick, can I just ask, you know, for the organizational reps, because the Committee always ends up hogging time, so I want to keep my mouth shut, but for the organizational reps, you know, could we bring in genetic counselors, could we

bring in SIMD, could we bring in all the other groups that are part of this Committee, maybe not as voting members, but as part of the Committee to help gauge the impact of your stakeholders? So, it's not just APHL having to do this Public Health System Impact, but can we -- maybe we need to think a little differently than what we've been doing to broaden the view and not just focus on -- I'm not -- I'm not picking on you in terms of you have to do all this work, but could we think outside of it -- what we've been doing the last several years to -- to bring -- to -- to gather everybody that's in that room -- I'm sorry I'm not there -- but everybody that's in that room to -- to get a better answer.

DR. JENNIFER KWON: Jennifer Kwon, Child Neurology Society. Yes, absolutely. I think that's what we need to do, especially I mean, I think it's interesting that Lisa brought up SMA as an example, and I think that it's an example that's worth remodeling based on the additional

data that we're getting from the clinical trials. I think that's really important because as we treat these infants who are being born, we are changing the phenotypes that we are used to seeing, and so, the only evidence that we have of efficacy and the proportion of later-onset forms of SMA, all that is becoming old data -- data that we're going to be losing. So, I really think this is the time, at least for that particular newborn screening program, to really engage child neurologists who are involved in treatment.

DR. CYNTHIA POWELL: Sue Berry.

DR. SUSAN BERRY: Sue Berry. Just a couple comments. I noticed in -- this is sort of a specific and then a more general comment. Scott, you mentioned in one of your slides that we ought to be adding the cost of therapy and follow-up costs to our consideration. That's certainly not something we have done previously, and by the same token, we have never considered the impact on the system we're generally beyond -- I know what

the -- what it said Public Health Impact but if we're really thinking about the system, we're not thinking about people power, we're not thinking about the cost and implications of longer-term follow-up, particularly as we add disorders with late-onset phenomenon. And so, I was excited when we started adding in the consideration of the Public Health Impact, but we really didn't ask a question about the system impact when that happened, I don't think, just about the test. And that, I think, is a little bit of what Scott was talking about here.

DR. SCOTT GROSSE: To clarify, I didn't say that I thought we should add those components. I said the Expert Advisory Panel members suggested that should be included.

DR. SUSAN BERRY: However you voiced it, it's not part of the discussion.

DR. SCOTT GROSSE: And I said -- but then -- right. But then the question was, is that feasible to do within the nine-month constraint,

and the answer is no. It's not feasible to include within the present process. It would be desirable to have that information, but it would require a separate process.

DR. SUSAN BERRY: I hear your careful parsing of this question, but it is not something we've considered.

DR. CYNTHIA POWELL: Organizational representatives, do you have any comments or questions? Yes.

MS. AMY GAVIGLIO: Amy Gaviglio, National Society of Genetic Counselors. I think this may be going a little off of what Scott said as well, but as he noted, it's not uncommon for us to see kind of that one to three year metric as to how long it's going to take to add a condition, but then we're only seeing maybe a third of states actually meeting that time frame, which suggests that the way we're asking the questions in the Public Health Impact Assessment perhaps is relying on too many assumptions and assuming in an ideal

state, which that isn't actually reflective of what the context with which we're trying to add conditions. I'm wondering if there has been consideration of trying to add some of that -- asking those questions of what else is going on in our public health environment that may preclude you from -- from adding a condition at, you know, under less than ideal circumstances, and if that could give us a better sense of timing for adding conditions.

MR. JELILI OJUDU: Yes. We just went through a revision of the survey itself, Amy, and again I think part of your question and something that Scott brought up earlier is collecting information that may be better suited not necessarily as part of this survey, but other information that's being collected. How we integrate that into the final package and how that information is being used to make a decision, I think is something that states do deserve to -- to know prior to going into this whole process,

because it takes time to respond to these surveys, and it -- the onus is on the state newborn screening lab directors or program directors to be able to move it around. I like the idea of making sure that a number of subspecialty groups are actually able to come together and provide more information on the system impact, but again, it's what that information is going -- how that information is going to be used to make that final decision that's important.

DR. ALEX KEMPER: I have a question for the Advisory Committee, but I don't want to preempt anyone else's question. So, Scott brought up something I think is -- is really compelling, and I thought that it would generate more discussion, so I'm going to bring it up again, which is a lot of work is put into trying to get like a fine estimate around the cost per screen, and it's very complicated given all the things that Scott talked about. So, one of the proposals that Scott had, which I think is a good one, is to

have a more qualitative assessment. So, instead of, you know, $1 per screen, have it be, you know, we can come up later with what the different, you know, cut points might be, but, you know, less than $1, $1 to $10, $10 to $100, you know, whatever it is. And I just wanted to gauge what the Advisory Committee thinks about that approach. This isn't obviously not -- but I just want to hear some thoughts about that.

DR. CYNTHIA POWELL: Mei.

DR. MEI BAKER: I think it's an excellent idea. I think just over time, I felt -- because different states have different situations. I'd rather give me a list, you know, the early adopters in what's involved, and also different states introduce a little bit different. For example, SMA, some states choose to do the digital PCR, do the SMA2 copy numbers. Some people may not. So, you list there, and you list there you say how much it's going to cost. Well, one state said I'm not going to have these items, so my

costs will be different. I think it's much, much better useful information than saying per baby, how many -- then, you also avoid in terms of different size states, because you can calculate yourself in terms of each items. I really think that I would really support this idea going forward, have this more quantitative and you have less because then you also overcome different diseases have different situations, like it depends on the technology used. So, you have second-tier. You can all include this, and people look at that, it much, much useful information, I think.

DR. CYNTHIA POWELL: Okay. I think Susan Tanksley, you were next.

DR. SUSAN TANKSLEY: So, sorry, I wanted to go back to the concept of collecting information -- more information from the system, and I like the idea of using the organizational representatives so that they can gather information from their perspectives. I -- as a

representative of a state newborn screening program, I know that when we do the newborn screening Public Health Impact Assessment, we attempt to go out, and we attempt to, you know, we'll send the survey out to like our specialists who are going to be seeing children for that disorder. We'll send it out to our Newborn Screening Advisory Committee. But it's hard for us to get a broader perspective, and often the information that comes back is completely conflicting. So, we'll have specialists from the same field who have very different views of how it's going to impact them. And so, I think it would be very helpful to have the broader perspective represented. And it's -- it's probably different questions completely from what's already being asked.

DR. CYNTHIA POWELL: Joan Scott.

MS. JOAN SCOTT: Joan Scott, HRSA. Alex, you had mentioned in your summary from the last meeting about some changes that might be made, and

I wanted to go back to one, because it does impact, I think, our conversation here, particularly around the modeling. And you had said that some of the recommendations, one of them was to include standard prespecified outcomes as well as the condition specific. And what I was wondering is have those been defined yet, or you were in the process of defining those.

DR. ALEX KEMPER: I was going to go back and find the slide. Of course, now I can never find it when I'm looking for it. But, so it's -- it's surprising straightforward to figure out the ones that we should prespecify that have come across all the conditions. So, it's really survival, you know. So, you know, death within, you know, whatever time frame, and it has been primarily around need for mechanical ventilation. Those are two things that generally come across. Now, more recently, we've done ones that affect neurodevelopment, and there -- there are a bunch of different ways going about that. So, we're in

the process of figuring out exactly that those things are. But I think that if we had a good measure of survival and need for mechanical ventilation and neuro or cognitive development, those would hit the big things, and of course it would be great to have, you know, quality of life measures and that kind of thing. But they just have yet to appear.

MS. JOAN SCOTT: Okay. Thank you. And ultimately, I think making sure those parameters are transparent and clear to everybody would be really important to everybody knows what's being looked at.

DR. CYNTHIA POWELL: Kyle Brothers.

DR. KYLE BROTHERS: I wanted to respond, Alex, to your question about the qualitative representation of cost, and my suggestion -- I'm also amenable to that. It seems to me that we want to weigh cost against benefit in some kind of general way that there's obviously no strict method for doing that. But a qualitative type of

thing could be useful there. But I wonder if it might be better instead of prespecifying qualitative categories to think about it as a confidence interval, and you could -- you wouldn't have to say it's 10 cents per child, but we don't know what it is. It's between 50 cents and $2.35, you know, something like that I think would be adequate. It might give you just a little bit more comfort in representing a number that you really don't know what the point number is. Yeah. And I have another question for you, Scott.

DR. SCOTT GROSS: Good idea.

DR. KYLE BROTHERS: Okay. And then, you mentioned earlier -- this kind of thing just ticks me off about the -- we have a contractual requirement, we're not allowed to give you the cost. And it just seems, I mean, absurd, but also in this context, that may be exactly the kind of disclosure the company would want. So, it seems like it would be -- there's a knee-jerk reaction that oh, it's in our contract, we can't tell you,

but really, if there was -- if states were to dig deeper, they would find out that maybe this would be a circumstance in which within certain boundaries they might be able to, if they just could talk to a human being at the company and confirm that this is okay. I don't know if you have a feel for that. I may be showing my naivety about those things.

DR. ALEX KEMPER: I'm going to defer to people who run newborn screening programs, but we're often told that they can't share those, it's proprietary.

DR. MEI BAKER: I think the term may be another priority. I think it's more confidential, right? Because they have to deal -- it's more business practice because -- so they -- the company -- I give you good price. It's not list price, but don't tell anybody else. It may be that.

DR. SCOTT GROSSE: It's not just newborn screening. The whole US healthcare system has a

lack of price transparency.

DR. BETH TARINI: Except the whole US health, as evidenced by the current political climate, the whole US healthcare system is not federally or state run, and these are state programs. So, having worked at two institutions that were public programs, proprietary -- I don't -- there are very, I believe, I'm not a lawyer, circumstances in which that proprietary information cannot be held back if it's state funded. It's -- at least, I agree -- it's at least something on face value that seems to not hold complete sniff test. That should be dug into deeper, given that there's federal and state dollars, federal probably coming through Title V to these programs, and then state dollars coming through as well.

DR. KYLE BROTHERS: Yeah. This is Kyle Brothers, and from the company's perspective, obviously every state in the country adopting a particular kind of test and them being in a

position to be able to help that happen, it seems like they could be partners in this kind of thing that that would be in their interest.

DR. MEI BAKER: Also, the state program, I can speak for Wisconsin, the newborn screening is through a fee system. We don't have state funds to do that. So, this is a -- to actually comes to the patients.

DR. BETH TARINI: So, you don't have any -- right. So, you don't have any Title V dollars, right?

DR. MEI BAKER: Not for newborn screening.

DR. BETH TARINI: So, right. If you had -- yes, if -- it would just be curious in a state -- in a situation what state touched -- let's say a program had federal dollars that it touched or state dollars, and it could be in follow-up, it doesn't have to be in lab.

DR. MEI BAKER: Yeah. Anything beyond 5,000, you have to put a bid. The bid you put in

maybe this is accessible information. I just --

DR. CYNTHIA POWELL: Susan Tanksley, I think you had a comment.

DR. SUSAN TANKSLEY: Susan Tanksley, Association of Public Health Laboratories. I was just going to state that, I mean, from -- from a state perspective, it may be the granularity of the question you're asking. So, we may be able to give you a lump sum number that has nothing to do with any confidentiality or anything; whereas if you ask for a very specific number, we may not be able to give you that very specific number.

DR. CYNTHIA POWELL: And taking the Chair's prerogative, Ann Comeau, I think, had a comment that you wanted to make and could I ask you to use the microphone and give your name and your affiliation.

DR. ANNE COMEAU: Thank you. Anne Comeau from Massachusetts. I think that there are a variety of these contractual kinds of things and they have begun to address them and some different

views of companies. So, part of the question that I would ask is what might a state expect to get back from contributing such granular data. So, if the granular data is going to drive companies to, for instance, have everybody get the same price for a particular reagent instead of the very big states being able to drive deals better than smaller states, that's something nice. But another -- another aspect is that some states to sell services, and if we're selling services, and if we are going out to bid against companies, then -- then giving very granular data puts us at risk.

So, if there is -- if we contribute such data and it can be de-identified, then -- then I think that would be -- if it can be de-identified and if the states who go to the trouble of working these -- working through very difficult data can do this, can expect to get some benefits from this, then you might get some more.

MR. JELILI OJODU: Thanks, Dr. Comeau. Point well taken. I -- we almost always do share

aggregate data, and, in fact, what you suggested is something that we certainly plan to incorporate or have started to incorporate into the information that we're collecting relating to cost. But highlighting the point of what we give back to the state and how it's going to be used is important.

DR. CYNTHIA POWELL: Okay. I think we're going to have to break for now. We are going to break for now. We will resume this topic after the break, and I'm going to turn things over to Catharine.

DR. CATHARINE RILEY: Thank you. Just again a reminder that as visitors, you have access to the pavilion room and the -- the fifth floor and the cafeteria, restrooms, et cetera. We will begin again promptly at 2:15. Thank you.

[BREAK]

DR. CYNTHIA POWELL: Okay. We're going to get started. Can everybody take their seats, please? All right. Thank you, everybody, for

your comments and discussions. We're going to continue.

[Speaking off mic.]

DR. CYNTHIA POWELL: All right. So, we're going to continue this momentum with a presentation from Dr. Kemper on assessing values, and that will be followed by Committee discussion.

MR. ALEX KEMPER: Okay. Great. Now that we've resolved all those easy issues -- that's a little bit of a joke -- we will dig into something bigger. I'd like to say that Dr. Bocchini, who was the former Chair of the Advisory Committee really, really pushed us to think about values, and he is still someone that we speak to a lot, and he's very much engaged in the process. So, I'm not sure if he's on the webinar or not, but I know that he'd be happy that we are talking about this issue today in terms of stakeholder values and decision-making.

It's a -- it's a challenging topic to talk about values and make sure that we're all on

the same page in terms of thinking about it, and so, I'm going to really begin with this at the 30,000 foot view, because really what we're talking about are the things that go into making an important decision. And so, when you think about it, there's certain things that you need to have for something to be an important decision, and then I'm going to use that to bridge to what we mean by values.

So, the first thing is when you're making an important decision, there have to be competing options, right? So, there's no, you know, if the only option is to do this if there's no real competing option, then there's no important decision to be making. So, in this case, of course, we have whether or not to add a condition to the -- to the RUSP, whether or not all newborns should be tested for a particular condition.

The second thing is you need to have outcome preference. So, if you have competing options but you really don't care about what the

particular outcomes are, if you're, you know, in a restaurant, and you can't figure out if you want to get the meat or the fish, and it doesn't really matter that much to you, then it's obviously not an important decision. But here, we do have important outcome preferences around the long-term health outcomes from the -- the newborn screens.

And then the third thing you have to have is uncertainty, and I think everyone knows from the discussion that we just had, there's a lot of uncertainty, right? So, we don't -- it's hard to predict necessarily what the outcomes of our decisions are going to be, but a lot of the work that we do is to try to understand and minimize the uncertainty.

So, at the highest level, these are the things that you have to have in order for there to be an important decision that needs to get made. And, of course, the outcome preference issue is where a lot of the value stuff comes into play.

So, going back to the conversation that

we just had with the Evidence Review Process, while we begin by describing the options, so we talk about newborn screening versus usual case detection, that's the stuff that Lisa Prosser does the modeling in primarily, but there are also sometimes alternative strategies for newborn screening. That's not something that we really face, but there are different ways to screen newborns for many of the conditions.

We characterize the outcomes. We look at the immediate outcomes of the screening, how many positives and negatives, and how many of the positives turn out to be true positives or false positives. We look at the individual level of health impact, so that gets to the things that we were talking about in terms of survival or need for mechanical ventilation or neurocognitive development -- those kinds of things.

And then we also, to the best of our ability, look at the impact on newborn screening systems. So, those are the kinds of outcomes that

we look at.

And then, in the Evidence Review Process, we outline uncertainty, right? So, we have, for example, range of test accuracy. Well, we're not entirely sure, but from the pilot studies that have been done, we think the sensitivity goes from here to there. We think the specificity is here to there. We think the number of true positives and false positives are in here. We talk about the distribution of potential outcomes, and then one of the things that we spend a lot of time in our final presentation is talking about gaps in the evidence. Where does the uncertainty lie that we couldn't answer with the Evidence Review Process?

So, this is how the Evidence Review Process currently addresses those three components of what goes into an important decision. I told you I was going to really go back and go to the 30,000-foot view, but this is the way that I can -- I sort of internalize the values part.

So, the challenges that we have in the newborn screening decision making is competing options, right? So, we're making these options about -- we're making decisions about newborn screening within public health, but it affects, you know, wide groups of people, individuals and their families. We have challenges around outcomes. So, we -- we give summary measures the population of benefits and harms. So, in general, for example, how many babies might be expected to live longer? How many babies will be exposed to harm? But we don't really -- that doesn't really get to what might happen at the individual level. We do look at issues and differences in timing, and this is important because often times, the harms of newborn screening and things like false positives may be proximal to the newborn screen, but the benefits might not happen until much later. So, there's this kind of funny thing where the timing of benefits and harms don't come out at the same time.

One of the things that's great about newborn screening is it helps decrease health inequalities. So, I think back to when the decisions were being made around newborn screening for critical congenital heart disease and it was Chris Kus who made the compelling argument that one of the reasons to make this part of newborn screening is to make sure that everybody has access to it. So, but that again doesn't really fit neatly within the -- how we consider things.

And then, there's also regret. So, there can be decisional regret. We wish we screened, or we wish we had done something like that, or we wish we had avoided a false positive.

There is uncertainty on both the benefits and the harms side with insufficient evidence to really minimize things, and part of it is things are fast moving. There's advances in both screening and treatment. I laugh because New York has provided us so much pilot information for many of the conditions, and inevitably before those

final votes, I also go to Michele Caggana and say you know, find any new babies today, you know? Do I have the most recent, up-to-date stuff? And, of course, there are all those trials. I neglected to say happy birthday to Michelle. I don't know where she's sitting right now. Maybe she's out celebrating. Everyone say happy birthday to Michele. So, and I apologize if it's anybody else's birthday. You can stand up if you want.

So, but things are fast moving. And then the challenge that many people have written about -- certainly Rod Howell has written about this -- is that you -- you have this problem with the benefit of early detection like beyond CLIR, but if you were to do the, you know, more pilot screening or implement screening more broadly, then you might be able to resolve some of this uncertainty, and how do you think about, you know, pushing screening forward when, you know, part of it is for this better sort of research side of things.

So, there are things that we can resolve partially through the evidence review, and then there are things that are just kind of, I guess you would say, ineffable, right? We can't necessarily resolve them.

So, that's where it's important to get stakeholder perspectives. That's pretty cool. Does it work on the big screen? Okay, I don't want to make anybody sick. So, I'm going to move past it.

So, I'm just going to read this quote about values from the guidelines GRADE, as I think most of you know is the approach to evidence review that's really given birth to a lot of the stuff that we do. So, from their work, "Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life. More precisely, they refer to the process that individuals use in considering the potential benefits, harms, costs, limitations, and

inconvenience of the management options in relationship to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of preference best captures the notion of choice. Thus, we use both words together to convey the concept."

So, I -- I hope that sort of gives a -- so, it was better written than anything I could come up with, and I am going to use values and preferences in the rest of my talk. And, you know, they talk about in GRADE looking at patient perspectives, and most of the work around GRADE is really for these kinds of individual -- more individual clinical decision-making and not the more public health stuff that we talked about.

But our -- the perspectives that we want to get go beyond the individual patient and families. So, I didn't want you to think that I'm being overly restrictive just looking there.

So, if you look at the process of going

from evidence to recommendation, GRADE does a lot of the stuff we do. They look at magnitude of estimates on important health outcomes, confidence, right, so we do that, estimates of typical values and preferences, we don't do that, and confident in those estimates, so how confident are you about typical values and preferences, variability of vales and preferences, and resource use. And we just talked a little bit in the cost part and in the Public Health System Impact on resource use. But, again, the issue that I want everyone to think about now is -- is how we think about values and preferences, how we can not only estimate them but understand the values -- understand the variability and what drives them as well, and then ultimately how we can use that in the decision-making process.

And just in case anyone thinks I'm going to have a slide at the end where I'm going to give the answer, sadly I do not. And so, I think we're going to be able to have a rich conversation

around that in a little bit, and it's going to be an ongoing conversation.

So, from our perspective, right, I'm going to lay out questions, and I don't think that we need to -- I'm going to go through the presentation and lay out a bunch of the questions, and then we can go back and revisit them. So, I'm going to encourage you to, you know, jot notes as we go through. But I think it helps to see everything first so you know kind of where we are.

So, who's values do we value, right, in terms of patients and family members and public health and even the general public who may not have a child. How do we figure out what values are we interested in. And then, related to that, how do we have a process so that we can understand the values of these stakeholders. How can we do that within the context of what we do as part of the Evidence Review Process? Again, I'm not sure. How can values and preferences be assessed, and how can values and preferences be incorporated

into the decision-making process. So, even if we were to be able to do this, how does it inform the process? Again, I want you to think about this. We're not going to go back to revisiting the matrix today. But it does help to think about like what's the ultimate use of values and preferences.

So, one of the standard ways in a quantitative manner to look at values and preferences it to look at utility, and from a utilitarian perspective, there's a measure called the Quality-Adjusted Life Year. So, one Quality-Adjusted Life Year would be like living a year in perfect health. It's a standardized measurement of health outcomes, and it can be used to facilitate comparisons across health conditions and across populations, because it's a standardized unit.

Now, I'm talking about, you know, qualities, but there are other similar measures and just for the purposes of the talk, that's why

I'm putting quality up here in case anybody is wondering, you know, why I don't have dailies or anything like that, that's why.

So, Quality-Adjusted Life Years is, as I sort of implied, is a function of time and utility, and utility can range from zero, which is death, to 1 being perfect health. Sometimes you hear people argue that things could even be worse than zero. But for the purposes of today, we're talking zero to 1. And there are a bunch of strategies for measuring utility, and this is not a method -- I'm not going to drill into this -- but it's time -- there's time tradeoffs. So, a simplistic way to think about this is, you know, if you were to go off and go to sleep and wake up and have the problem gone, you know, how much time would you be willing to trade off to resolve the problem. There's a standard gamble where you can trade off having the health condition that's under consideration versus, for example, death and life and, you know, what -- what -- what risk would you

be willing to take between dying and living versus having the condition. And so, there's an iterative process that you can do at the individual level called the standard gamble. There's the visual analog scale, where you have like, you know, zero here and 1 here, and you ask someone what they feel about something, and they can put a dot in there. The visual analog scale is not the most rigorous thing as it turns out, like if you change the visual analog scale from this way to that way, people put different answers. People talk about there's like psychological gravity. People tend to go lower when it's up and down. And then there are other standardized quality of life instruments, and they can be converted to things like qualities.

There's lots of issues with qualities. I'm not here necessarily to defend qualities, but I want to put qualities up there as one measure, and I'm looking over it as Lisa Prosser and Scott Grosse, who I'm going to ask them to answer any

difficult questions anybody asks about qualities.

That being said, I think it's fair to show some qualities that appear in the literature, just to show how they can be kind of funny. So, this is a study that was done by Anna Carroll and Steve Downs that was published in the Journal of Pediatrics ten years ago now where they just kind of went all around Indianapolis to practices, urgent care centers, health fairs, and even the Indiana State Fair, just getting convenient samples of individuals just to get a sense of what utility they put on things and use the standard gamble. And if you go to the article, they have like lists and lists and lists of things that people wrote about different conditions.

And I picked four things that were chronic diseases just to kind of show you when they did the standard gamble. So, living with mild ADHD had a utility of 0.94 with a range of 0.72 to 1.0. so, that's a pretty big range and, you know, I kind of think like well mild ADHD,

maybe I have mild ADHD when I look at how I get things done. But, you know, is that -- how big of a deal is that?

Monocular blindness. So, imagine being blind in just one eye. The range in there from the 5th to the 95th -- so, the median was 0.88 with a range of 0.5 to 1.0. So, that's a huge range, and I kind of think about like if I were blind in an eye, like, how terrible would that be, you know. But I'm surprised that that's below mild ADHD and the numbers they got.

Severe bilateral vision loss. So, that's being blind in both eyes. Actually, it didn't seem that far in terms of the median from being blind in an eye.

And then, severe intellectual impairment, as you might guess, had a much lower utility with a very wide range from 0.1 to 1.0.

So, the reason I put this up is just to show how much variability there can be in utility assessments and, you know, nobody has to share

with me what they think, but think about how you feel about, you know, where you might fall within these things.

So, beyond that, there are challenges in figuring out utilities. So, understanding a health condition, right? So, you can't really give a, you know, report your utility on something unless you really understand the health condition, and a lot of the health conditions that we're talking about are really complicated. It's important to understand the perspective. And there are also all sorts of contextual factors, factors outside of the condition itself that could affect what the utility is. Again, at the end of my talk, maybe I'm going to invite Scott or Lisa to see if they have anything else to say about quality or utility assessment.

So, there are other ways of getting utility, and one of the things that I got really excited about after we had that in-person meeting was this notion of a citizens' jury. So, a

citizens' jury -- the notion is you pick a group of people that are representative of the public. They typically have up to 20 people, and it's kind of like Grand Jury. You give them tons of information and substantial time to deliberate -- as much time as they need, and let this group come and let you know how, you know, the range of values or what they think ought to be done. Obviously, there's substantial risk of bias if that's not done properly, and I think, you know, all of us have seen, you know, like the focus groups that they do on the news around election time to show what the public is thinking about, you know, candidates and that kind of thing. You know, it probably makes everyone break out in hives. But, that being said, if you do the citizens' jury thing right, it can really be informative, and they've been used in Europe and in Australia for all sorts of things.

So, I'm just going to read this list, because I think it's so interesting. Legislative

reform of insurance for injury compensation after motor vehicle collision, taxing soft drinks, ethics of mitochondrial donation using assisted reproductive technology, extend of patient control of their medical records for research, cystic fibrosis carrier screening in Italy, bariatric surgery in Australia, government funding of adolescent vaccinations, and screening for prostate cancer in Italy. So, other groups have used citizens' juries, but the -- when you read these articles where they talk about the use of citizens' juries, these citizens' juries got, you know, weeks and weeks and tons of information about it, and when you think about newborn screening, even though I was like initially excited about this idea, the -- the practicality has sort of come into play.

Another method is this issue of using public surveys, and I would like to acknowledge Committee member Dr. Beth Tarini, who has done some of this survey kind of stuff to get a sense

of public preferences around newborn screening. So, they are certainly more feasible to administer surveys to a nationally representative panel. Now, that's not to say it's easy, but it's more feasible. And depending on how you set things up, you can assess preferences using sophisticated approaches like those that are used in marketing. You know, these -- not like a simple, you know, like Survey Monkey kind of thing that we get, but things with real logic that can, you know, drill more deeply into preferences and values. And, you know, it was interesting because, you know, I don't know, Dr. Tarini, if you want to stop now and comments on this, or if you want me to keep going. But this was a study of adults asking them about characteristics related to newborn screening that they, you know, think are important. And just pulling from the discussion section, the impact of newborn screening on treatment success was not associated with the recommendation for or against newborn screening for a profile condition.

I'm quoting that, I think, correctly. And that cost was the most important attribute, and then the age at which treatment would start. And, you know, it sort of flies in the face of a lot of the kind of more policy stuff that we talk about, and there's reasons that that could come up. I mean, certainly, that could just be what people think, but also it's sort of the challenge too of training people to think in a -- in a public health perspective is also challenging.

But I think that this -- this report is particularly important, and I would encourage members of the Advisory Committee to take a look at it. Dr. Tarini, I don't know if you want to comment on this or if I should just keep going.

DR. BETH TARINI: Just to thank Dr. Prosser, who had the AHRQ R01 that funded this project, which I was the co-investigator, and she is the senior author.

MS. JOAN SCOTT: Can I ask a question since we're pushing pause on here? Was this a

discreet choice of methodology?

DR. BETH TARINI: It was -- go ahead. This is the expert.

DR. LISA PROSSER: I just want to make a couple of -- thank you -- comments about this paper, because --

DR. CYNTHIA POWELL: Please state your name.

DR. LISA PROSSER: Lisa Prosser, University of Michigan, thank you. So, this survey, one of our conclusions after going through this process, it was extremely difficult to frame these questions in a way that the public could answer them in a reasonable manner, and, in fact, we're presenting in this -- in this paper the results from the best, which worked much better than the discreet choice experiment, which part of our conclusions was that that part of the survey really did not work well. And one of the conclusions that we come to in this paper is that a citizens' council or a citizens' jury approach

for newborn screening would likely be much better because of the extreme complexity of the process. We have used this technique well in other public health interventions like vaccines where people have a baseline knowledge of that decision-making process. But here, they really need much more of an introduction, and that's very difficult to do in a 15-minute survey.

DR. BETH TARINI: Thank you.

DR. ALEX KEMPER: Anything else? Okay. Any other questions about the study in particular before I keep moving on? Okay.

So, one of the things that our group and certainly K.K., Ashley, and I talk a lot about is this notion of multi-criteria decision analysis, which builds on top of all the things we have been talking about. So, I'm going to highlight one particular multi-criteria decision analysis process, not because I necessarily think it's the best, but it's the one that we know the most about, and we've, you know, in the past spoken to

representatives of the group. It's called EVIDEM, and they look at the value of an intervention by domains including the need, comparative outcomes, economic consequences, knowledge about the intervention, and then what we're talking about today, population priorities. And they have this like very complicated model of points and that kind of thing. But the key thing is it's -- it's a process that pulls together these different things within different domains as a way to make sure that you're thinking systematically about all the components that need to be considered, and it's also, I think, a nice framework for explaining the different attributes of a decision.

So, again, just reading from their work, it's situated within contextual factors such as alignment with priorities. This gets to a lot of the stuff we were talking about in newborn screening parameters before, environmental sustainability, system capacity, and the political, historical, and cultural context. So,

obviously there's a lot of stuff that goes into decisions.

So, the EVIDEM framework when they look at value, looks at -- at need for the intervention. So, how bad is the condition, what's the size of the potential population, what are the current unmet needs, what are the comparative outcomes, what are the types of benefits, is it a preventative service or a therapeutic service, what are the economic consequences both medical and nonmedical, how certain are we -- they talk about the knowledge, about the intervention including the degree of evidence and expert consensus, and the do have a scoring system that has been adapted for rare disease, not newborn screening, but rare diseases that affect adults.

So, here's an example of therapeutic interventions that have been assessed using EVIDEM, so pulmonary arterial hypertension, gastroenteropancreatic neuroendocrine tumors,

which again is not a pediatric thing necessarily, non-Hodgkin lymphoma, thyroid cancer, dementia, and Prader-Willi syndrome.

And then on the prevention side, there may be other things, but what I was able to find was looking at comparing different methods of cervical cancer screening in South Africa.

So, I think I've probably opened up a lot of questions that you all have, none of which I'm probably going to be able to answer. But I'm going to just throw in other things to think about. So, first of all, I think that, as with everything that we do when we start gathering data, it's starting from square one, why assess these and how is it going to be used in the decision-making process, who are our stakeholders, what values and preferences are needed to facilitate the decision-making process, so maybe we don't need to evaluate everything, or maybe there are certain values and preferences that we can assess, even in the absence of, you know, like

a particular newborn screening condition that would like carry through and that you could reuse, and what are the key points that are needed, how can the relevant values and preferences be elicited.

So, we talked about some methods, and again thinking about the review process itself and maybe this is like self-serving, but just to think about the constraints that we're in when in the review process, should values and preferences be elicited. And, like I said before, I think that there are probably some things in general that we might be able to work on ahead of time and, you know, have kind of a plug-and-play for certain things. But there are going to be a lot of condition-specific things.

So, now I have asked a bunch of questions and I'm a little nervous standing here because I don't know any of the answers.

DR. CYNTHIA POWELL: All right. We can open this up to Committee members first. Melissa.

DR. MELISSA PARISI: Melissa Parisi, NIH. So, I'm really intrigued by this notion of a citizen jury and how that might be incorporated into the review process. And I guess I'm thinking out loud here, would you conceivably include family members who have some familiarity with the condition? Would you want people who, you know, would just come in blinded and not have familiarity with newborn screening or the condition and then basically give them the same framework of educational information? And could that be done at a process of the evidence review that you would already have some of the basic evidence gathered, but perhaps at the same time when you're doing the public health assessment such that if it took, I don't know, several weeks or it was a series of conference calls or something along those lines, you could actually incorporate it and include it in the reporting back.

DR. ALEX KEMPER: So, like I said, I

don't know any of the answers, but I'll tell you what I've been thinking about. So, I got really excited after our in-person meeting about the notion of citizens' jury, and then, you know, when you think about them supposed to be broadly representative and, you know, who exactly should be on it, you know, parents or individuals with the affected condition versus the general public, I -- I sort of like, you know, wilted under the pressure and got nervous that that was going to be feasible to do, especially with how much work it takes to educate people. But, this is one the things where I was going to call on Lisa as well because I know that you've spent a lot of time thinking about it. I know if you -- do you want to come up here so people can see you better?

DR. LISA PROSSER: So, I think, you know, leaving -- leaving aside for now the practical and logistical considerations, I think, you know, ideally if we could incorporate both the patient and family perspective as well as the public

perspective, that that would really enhance the process. And when we think about health technology assessment, we typically view those as two separate but very important views in the process. That the patients and families, you know, have a perspective, that they have experienced these diseases, you know, in the broader literature of evaluating health conditions from, you know, all different types of health. Public values -- people that thinking about imaging a health condition tend to place different values than people that have experienced the condition or -- or have a family member that's experienced that condition. But both of those perspectives are typically important, especially when we're thinking about a public health program that will be, you know, is being funded, you know, at the public level.

MS. JOAN SCOTT: Just to both of those perspectives -- sorry, Joan Scott, HRSA. Both of those perspectives are important and potentially

different. In a citizens' jury format though, with only 20 people, are you suggesting that those would be incorporated into that --

DR. LISA PROSSER: I would suggest we have two.

MS. JOAN SCOTT: Yeah, okay.

DR. LISA PROSSER: Two, yeah. And you could set up, you know, two citizens' juries, not that they can't ever talk to each other -- actually it might be quite interesting to have some cross-talk among those groups, that if you set them up over -- typically they have a standing term, you know, of two to three years. And so, it's not as if, you know, on the public surveys, you know, we're trying to educate people at a single point in time every time we ask them a question, and here they would be able to have the background and the context of this whole decision-making process when new conditions come up.

DR. CYNTHIA POWELL: Beth.

DR. BETH TARINI: Beth Tarini. To remind

the members of the Committee that the Iowa Newborn Screening Program held a citizen jury about their newborn screening that Kim Piper and Dr. Michelle Gornick led, and I believe Kim presented to the Committee on the findings -- I don't -- I wasn't involved -- which were there -- there were diverse and at-odds in some -- it was just as ours found, if I remember correctly, but I don't want to quote it directly.

UNIDENTIFIED FEMALE SPEAKER: Was it general public?

DR. BETH TARINI: It was general public.

DR. CYNTHIA POWELL: Natasha.

MS. NATASHA BONHOMME: Hi, Natasha Bonhomme. I have two comments. One is, I think it's great to be discussing ways to incorporate both the public perspective as well as those who are affected or, you know, touched by a condition more closely. But I don't honestly think that those are the only kinds of public things that we lump into public or advocacy groups. There are

also organizations that look at the trends the same way that you can have a pediatrician on a panel, but then you can also have a representative of EAP that may be looking at trends in the field. So, I -- I think sometimes we distill all the groups just into public/advocate/family and that there may be a lot of others in the context, and this is more a comment not just for this piece but the discussion of the entire afternoon. So, just wanted to note that.

And then, I also wanted to -- I apologize, I don't know if this is a question or a comment -- but just some discussion around what does it mean to be assessing value and the decision-making process in a mandatory program. I think that is something that often times comes up, especially when we're talking about educating and engaging people, but the concept of decision-making is that there is a decision to make, and a mandatory program depending on how someone interprets that is that there is less of a

decision to make. And just as we're bringing up these different words, just what does that mean in this context.

DR. LISA PROSSER: So, can I comment on this -- or to comment on the stakeholder groups, I think that's a really important point, and during the EAP meeting, we did discuss to some extent that there are many stakeholder groups who may have values and preferences about this process. But the discussion really focused on that the most important groups that we're not including right now, at least from our discussion, and I think that's for the Committee and others to discuss as well, are the patient/family preferences and public preferences that we don't have those incorporated into the process. I'll let you add to that.

DR. ALEX KEMPER: Can I just attention add -- sorry, but I just -- so, you know, we have a really big country too, and I always worry about when there's like one or two families that are

supposed to represent the few points of all families or in this case, even 20 families, especially when you think about the, you know, the rampant disparities in our healthcare system even beyond the, you know, individual differences in perspectives. And I will say, you know, MCHB has done great work in addressing disparities that we have in our healthcare systems. I just wanted to acknowledge that. But it's just really hard for me to figure out who -- how, you know, in a country of whatever it is -- 300 million people -- that we have this kind of generalized thing. There's again probably a solution to that if the, you know, if this is the approach that will be used, but I just think it's really important to get in there, and I think, you know, Natasha, you raised the question of what's the decision. Well, I mean, the decision ultimately is whether or not individual programs added onto their newborn screening program not at the individual level when something is added to newborn screening unless

people opt out, and obviously we don't want that to happen. But I think that's one of the reasons why it's so important to assess these values and preferences and incorporate it into the process.

And it could be that, you know, at the end of the day, different methods will have to be used in terms of, you know, these are not exclusive, right? So, you could have a citizens' jury, you could also do some sort of other online approach, expert advice, you know, point scaling like EVIDEM would suggest. I mean, it could be amalgam of things. But these are all really difficult questions. I'm sorry, I didn't mean to preempt you.

DR. CYNTHIA POWELL: So, next we have Kyle and then Annamarie, Robert, and Beth. Kyle.

DR. KYLE BROTHERS: I think -- I feel like I'm still kind of forming my opinions about this. It's such a complex set of considerations. Just from the perspective of thinking about this is a Committee that's supposed to make decisions

and should be hearing from stakeholders, and then what does it mean for someone else at some other point in time to hear from stakeholders selected in some way and then represent those preferences and values through some kind of report, and how do we distinguish between those two sets of information and how we balance them. I mean, it becomes -- I mean, this whole process is about rhetoric in some ways, right? It's about -- it's not so much about understanding what the values and preferences of stakeholders are, I think that's really quite important, but the decision-making of this kind of body seems to me to take into account the sort of rhetoric from the perspective of what are the techniques or methods used to convince another person to think something, right, or to agree with you. So, just thinking about, you know, the really compelling stories that we hear from families can be very convincing. That's a very convincing kind of rhetoric, right?

But then thinking about, you know, what about the false positive families, and they don't really get together as kind of an advocacy group. They just kind of like randomly pass through this false positive process, and then they kind of go on with their lives. But they have a perspective, and it would be really hard to hear that perspective. So, I guess what I'm saying is I'm still trying to think through what it would mean for you all to bring values and preferences as a part of a report versus -- and representing other perspectives to us versus us as a Committee being in a position where we have to make a decision and consider stakeholders directly speaking with us. So, anyway, no answers there. There's just a lot of complexity.

DR. ALEX KEMPER: Well, and I'm going to channel my inner Joe Bocchini. I mean, part of the reason that he wanted to push forward with his notion of assessing values was to be able to reach beyond just the group of individuals that -- and I

don't mean to minimize, I mean, they're incredibly important, but to make sure that there's more holistic assessment of values and preferences, and that's one of the things that gave birth to this whole thing.

DR. KYLE BROTHERS: Yeah. In that case, I think citizen jury might not be the best context, because it could be that there are rather isolated kinds of perspectives like the true positive perspective just as an example, but there could be others that it would be really hard from 20 people or 50 people or 100 people or ever 1,000 people to really get the perspectives -- to really get a holistic view of the perspectives.

DR. ALEX KEMPER: I'm just going to jump in. Somebody's listening in and typing. So, if you're typing, put your phone on mute.

DR. CYNTHIA POWELL: Yeah, I was going to ask -- is there someone on the phone line who wants to make a comment, in which case, I'll add you to the list. If not, could you mute your

line, please?

DR. LISA PROSSER: So, I will respond by saying that I think that what the value -- the value of adding values and preferences would be is that we would move from the individual experience to more of a group perspective. And again, given that we have a very large country and we're still going to be only including a select number of individuals there, I think viewing this from the perspective of, you know, this is a process of health technology assessment, that the discussion that was happening was that there is this very important group of stakeholders, and we hear from them to some extent, but is there a way that we can systematize and better reflect that group perspective for the Committee. And I don't know that we've settled on a specific process for that, but that's the goal.

DR. CYNTHIA POWELL: Annamarie.

MS. ANNAMARIE SAARINEN: Thanks. I may have -- I'm not going to be very elegant here,

because I've kind of lost what I initially wanted to say as a follow-up to Melissa's comment, and I just wanted to say how much I appreciate you, Melissa, because you were saying exactly what I was thinking at the time. I think the processes that you were outlining, Alex, could be incredibly useful and, like you said, they don't need to be done in a vacuum. You could do a citizen jury in one state and maybe look at a different method in other states.

But if you look out into the real world, there are focus groups, for lack of a more medical term, conducted every day among the private sector when they're developing products and services, and part of having a focus group is trying to get a representative sampling so that you know how different audiences that might want that product or service will respond to it. And I think if you sort of watched how things have progressed over the last 20 years or so when it comes to vaccines, there are some really important lessons to be

learned there, both on the plus side in terms of communication and advocacy and outreach, and on the not so plus side. I'm sure if you asked a person about their perception of vaccines, if their children had them on schedule and had gone through their process that they would be, you know, have a completely different perspective than someone whose child may have had a vaccine injury. So, our perspectives among families who are impacted by conditions, I think we all know how important that perspective is. And how will that -- like, let's just say if you're trying to -- and I'm not sure you were trying to say that this was something you would do -- but if you're trying to equalize the perspective of families who have children impacted by conditions with the general population, then that would be a difficult thing to do, because 20 people in that one group and 20 people in the other group, I think that wouldn't be useful for us as a Committee to be taking that information and trying to input it into a dataset

that allows us to make these decisions. But I really appreciate all the thoughtfulness that you've all put into us thinking about this so that stakeholders are more broadly represented in the process, and I think the end result will be something better.

DR. LISA PROSSER: Great. Thank you for that comment, and we didn't mean to in any way intend to create a process that made any kind of value judgment about the, you know, the contributions of those different perspectives. And, in fact, part of our conversation was that to make sure that there was a more complete representation of the perspective of patient and families integrated directly into the assessment process. I think that -- I say I'm speaking for myself for these next few comments -- but that if we think about the evaluation of the evidence review that we do now, it's primarily quantitative, and that this would really bring into a qualitative perspective and I'd really

appreciate your comments about focus groups, because that's exactly what this -- whatever we decide here, that's the objective of that, to bring that kind of qualitative information into the Evidence Review Process.

MS. ANNAMARIE SAARINEN: And just one quick note about the amount of time and energy that Baby's First Test and Resources I think have put into kind of understanding the general public perspectives again on newborn screening. I mean, this goes back to, I don't know, Natasha, like ten years ago, I think. There's probably still some really, really relevant data there, yeah, that potentially isn't condition specific or maybe they even have some stuff that's condition specific. But I think there are some things there and what Beth said that was done in Iowa. I mean, there's things we can draw from.

DR. LISA PROSSER: Um-hum, absolutely. Absolutely.

DR. CYNTHIA POWELL: Robert.

DR. ROBERT OSTRANDER: Bob Ostrander, American Academy of Family Physicians. I'm going to touch on a very specific part of the evidence review and decision making and how it dovetails with this, I think, partly as an example and to get your thoughts on how one solves this type of dilemma.

So, what I want to talk about is when the Committee and the Evidence Review team has uncertainty about the benefits of pre-clinical detection of a condition. It's something we see all the time in primary care adult medicine, but we have this issue with cancer screening, and there is a big value piece to this. If people have early detection, it doesn't necessarily change -- and it truly doesn't necessarily change the outcome. The value preference when someone has clinical symptoms is I'm sure glad we caught this early because now I know that everything was done that could have been done, even though in reality that didn't really change the outcome or

initiation of treatment.

On the other hand, if you diagnose somebody in the pre-clinical phase, the harms of early detection are very real, as simple as losing good quality of life years worrying about when the shoe is going to drop, and I went through this with a kid with pre-leukemia once on the pediatric side. We go through it all the time with people with, you know, PSAs that are abnormal waiting for the shoe to drop and then the other harms of, you know, maybe starting treatment early that are toxic because you've made the diagnosis and you've robbed people of the blissfully ignorant high-quality lifetime they have. And I think you're going to have a hard time getting focus groups and -- and, you know, clinical or, you know, juries to necessarily understand or see that, and how do we wrap our heads around, you know, the harms of early detection and including that in our value matrix when it comes to these situations where there's a question about the value of early

detection. I hope that was clearer than mud.

DR. ALEX KEMPER: Well, I'm going to -- so, you're right. These are really, you know, difficult clinical questions that come up, and I just want to drill in to make sure that we understand your question, and then I'll going to make Lisa answer, which is how do you make sure, like if you go to the citizens' jury perspective, that the -- that the individuals who are on that understand the kinds of things they're weighing off against one another. Is that -- is that your question? Or just that in general these are really difficult things to do?

DR. ROBERT OSTRANDER: What I'm -- what I'm -- my question is, is how do you get the awareness of the harms of preclinical detection into the discussion, because I don't think that's something that non-clinicians -- lay people can wrap their head around very much, partly because, you know, everybody in my generation and older grew up with, you know, here's the eight signs of

cancer, and early detection is the key, and they think that about everything in life. So, how, you know, how do you -- how do you get that into the discussion so that it's given equal weight to the other side, which is the benefits of early detection, because, I mean, that's the struggle I have all the time, and I think it has a really, really big value. I think if people understood that value, they would have a little different vote on their citizen jury. So, how do you -- how do you --

DR. ALEX KEMPER: So, I --

DR. BETH TARINI: Can I jump in? Because I've actually been on a citizen jury.

DR. ALEX KEMPER: Okay, yeah. Why don't you --

[Simultaneous speaking.]

DR. BETH TARINI: You've been in one? You've been in one?

UNIDENTIFIED FEMALE SPEAKER: Go ahead. No, I haven't. But I have comments about how we

see this play out.

DR. BETH TARINI: I have facilitated as part of a citizen jury -- oh sorry, Beth Tarini, Committee member. I've actually facilitated a citizen jury at the University of Michigan that was on designating authority to a surrogate on Alzheimer -- participation in Alzheimer clinical trials. Like, it was hard to get more complicated than that, and these people did not necessarily -- they were taken out of the phone book, like they did not necessarily have anything. So, how did they -- to your question -- how did they do it? They very carefully -- Dr. Kim, who is now, I believe at the NIH, Scott Kim -- very carefully constructed a series of lectures and question and answer sessions which touched on all of the issues there. The speakers were very well prepared, you know, it wasn't -- there was no persuasion. The factor of persuasion was mitigated to the best of their ability, and the facts were presented, and all of the sides were presented, and then they

went through one by one. And I can tell you at the table anecdotally, I was impressed that they were able to -- what the public was able to pick up from the beginning to end. But everything was very well curated. He actually likens it to preparing a wedding. It is so highly orchestrated and curated. You would not believe the amount of work that goes into it.

DR. ROBERT OSTRANDER: So, without that, I probably wouldn't want to trust it.

DR. BETH TARINI: What did you say? I'm sorry.

DR. ROBERT OSTRANDER: Without that, I probably would not want to trust it with something where there's --

DR. BETH TARINI: Right.

DR. ROBERT OSTRANDER: -- where there's this -- where there's --

DR. BETH TARINI: It was an R01 funded NIH. So, I think --

[Simultaneous speaking.]

DR. ROBERT OSTRANDER: But, you've got -- there's certain areas that there is implicit bias and this lead time thing is one of them, and in order to overcome that with a citizen jury, you're going to have to invest time to bring them kind of up to our level, if you will --

DR. LISA PROSSER: I think so.

DR. ROBERT OSTRANDER: -- and I wouldn't trust if that wasn't done.

DR. LISA PROSSER: I think so, and that -- that is the advantage of having a citizen jury in a context like this, because it would be a standing group that you could educate over time as opposed to a one-time focus group. I agree it's similar to our public survey, extremely difficult to get people to try to understand, you know, these concepts. But they can get there and it will take careful planning -- that's a great description.

The other piece of that is to recognize -- and I think this is the piece that would have

value for the Committee -- is that there is real heterogeneity in preferences around things like early detection, and that would be important to be a part of the conversation here.

DR. CYNTHIA POWELL: Joan.

DR. BETH TARINI: Did I -- oh, was I on the list because I just jumped in. But I have -- I wanted to say, sorry, Beth Tarini, Committee member. First of all, Dr. Gornick from AKIAC [phonetic] gave me the three bullet points from that meeting -- from the -- the work -- she says she believes it's under submission, that the public was not for adding everything, actually, in their discussion, that they wanted more communication before the baby was born regarding what newborn screening is, what was on the panel. And they focused on specific conditions, but the point was taken that screening for everything just because the technology is there was not lost on the public. So, further -- again, this is her perspective having run in partnership with Kim

Piper, the head of the newborn screening program in Iowa -- that program that these -- these -- these complicated issues are not lost on the topic, and on the public. And I want to say that I do think that with time that the public is -- they've lived some of this. They've lived mammograms. They've lived prostate screening, especially the older members of the public. So, I -- I think that there's -- as a physician, sometimes we think it's just too complicated for the public to understand. But I think if done well, some of these complex issues can be communicated, and the public can understand them.

That being said, I want to remind the Committee and the community that this is a shift. We are talking about now -- when we say public at this meeting, immediately I would say many of us think advocacy groups. When we say public in a citizen jury, we mean like going to the DMV, right? And so, this is what you're going to get in terms of perspective. And so, the other

question I have is -- I'm not saying it is or is not a good idea -- is that what are we going to do -- if -- we need to be comfortable with the information we get, because if the public tells us it's not worth the money to screen, are we going to say okay, well the public just doesn't understand. If the public says we should screen for something for which there is no treatment -- the information is the only -- there's no -- there is no modification of symptoms that the benefit is to the family or that information is the benefit, are we going to maintain a mandatory newborn screening system? So, we have to both be aware of the potential data that we get, and we, you know, what -- that we respect what we get, and how it fits within the structure of the system which is currently a mandatory state-based newborn screening.

DR. CYNTHIA POWELL: Joan.

MS. JOAN SCOTT: Everything Beth just said. I want to corroborate what Beth just said

about the complexity of the information, because I participate -- I've run some of not exactly citizen jury but citizen-like jury things, and it's interesting, approval often goes down over time as individuals learn more about the, oh, well I never thought about, oh, hmm, ah. And so, approval often can very easily go down. So, but -- and it can be very complex and nuanced information, but it does require a lot of resources and efforts to get to that point. It is not a trivial undertaking.

So, you know, one of the things I wonder is if -- a couple of things have been suggested here. There is information that is out there that has been done over the years in different context, and I think it would be useful to compile and hear about all of that -- about refresh ourselves on, you know, what we -- what is known about preferences in this area. And -- and I'm wondering if there's also a potential role though for -- maybe not for every single condition --

would there be information that, using one of these approaches, that we could find out about -- about where the pain points are or what are the criteria by which individuals judge these things as opposed to every single -- the nuance of every single condition that may come up. So, that's another -- that's another potential approach. [Simultaneous speaking off mic.]

DR. BETH TARINI: This is what Dr. Prosser -- in the survey we did, right? I don't know if you want to speak to it.

DR. LISA PROSSER: Go ahead.

DR. BETH TARINI: Beth Tarini, Committee member. We had -- we only had 15 minutes to explain, you know, how long we took the survey online. But what we did was aggregate the disorders as best we could and the types of disorders we knew of and could imagine as well as the treatment and everything into -- what's the word I'm looking for that we always use to use?

DR. LISA PROSSER: Attributes.

DR. BETH TARINI: Attributes, right. Like, you know, these can be aggregated up, if you will, into something that is serious and deadly but manageable early or, you know, has -- when the life span peters out, when the symptoms come on, all of these attributes is I think what you're saying, Joan.

DR. ALEX KEMPER: Like exemplar conditions, because you can imagine there's like congenital hypothyroidism, there's SCID that represents -- you know what I mean, like this different -- PKI, you know, these conditions that are similar to a lot of other ones.

DR. CYNTHIA POWELL: Kyle.

DR. KYLE BROTHERS: Yeah, this is Kyle Brothers. I'll just start off by saying I'm a qualitative researcher, so I have that bias, but on the other hand, I'm also an ethicist, so I'm always -- one of the issues I think about a lot is to what extent do we let public view, as something I said earlier, affect an actual decision, you

know, in terms of what weight does it carry, how do we decide what kind of weight it carries, all those sorts of things.

I just wanted to point out two things that we should consider. One is that there -- there's sort of extensive evidence throughout the history of humankind that stated intentions, preferences, et cetera under a hypothetical situation can be very different in comparison to a real situation and so, you know, you think about a family that has actually been through a disease -- that is a very powerful piece of information, because they have actually lived it, and they understand that. If you ask someone to hypothetically imagine what would it be like, it might come to a very different kind of result, even after a really careful deliberation, you know, of the information being presented. It's still a hypothetical to them.

And two, that it seems to me there is, you know, the kind of qualitative research I do,

it's typically we're really trying to understand what the experience of a person is, what they -- how they feel about something, and there's really no decision at the end of that. We're just trying to understand what's going on. It's kind of a neutral kind of qualitative research. But this is the kind of research where there is this kind of -- it's not -- we're not neutral, and I'm just kind of trying to find out what people think. There's a decision that has to be made at the end, and I could imagine that that would also influence the kinds of information that we get. So, I might say something -- if you just think about, you know, the election going on, if you were to randomly call someone and say who are going to vote for and why, that would be very different from calling Cory Booker and asking him who he's voting for and why, right, because he, you know, he has a -- he's invested in a particular kind of decision, whereas a random person is not. And I could see that that -- this kind of dynamic where we're trying to make

a decision as a result of this information could influence what we're told, and we should think about that.

DR. BETH TARINI: This is Beth Tarini. I don't know that it's -- having done qualitative research but not to the level you have -- I don't know that it's really a qualitative study because it's not hypothesis generating. It has qualitative attributes to it, right, like it is an intervention. I mean, at its core, would you say it is an intervention that has -- of which the intervention packet, if you will, has these qualitative, I mean, you're giving information but because you're coming through a human, it has a qualitative lens. And at the end, you have -- and you have a metric. Before you're going to vote and at the end of you're going to vote. So, it -- it's -- it's not qualitative exactly in the same way, and I -- but I do see where people get concerned that like, well I don't what the biases are, right? I don't know -- because I can't

measure it and I can't see it, and it depends who speaks. But at the same time, I -- I would just pause it that it's not as free-flowing cowboyesque and it's not as qualitatively generative, you know, as a qualitative interview would be or as a focus group. There is certainly discussion at individual tables, for instance, that occurs. But -- and there's interaction, but it's not totally qualitative.

DR. ALEX KEMPER: And I was just having a sidebar with Lisa, because, you know, another way to think about it, this is one more data point to inform the Advisory Committee's decision. So, you know, at the end of the day, the question is, you know, does the Advisory Committee want to vote without having an understanding of the values and preferences, or does one have it? Do you know what I mean?

DR. BETH TARINI: I think it depends on what the answer is.

DR. ALEX KEMPER: Well, I -- right. But

I'm just saying that that's -- that's how that information is going to be used is -- needs to be sorted out. But ultimately it's, you know, whether you want to have the information or not.

DR. CYNTHIA POWELL: Natasha, did you want to come up?

MS. NATASHA BONHOMME: [Gestures no.]

ADJOURN:

DR. CYNTHIA POWELL: All right. So, with that, thank you everyone for this discussion and your comments and presentation, Alex. So, we're -- I want to make sure that everyone has time to get to their work group meetings and the locations are going to be on the screen. There we go. Okay. And I look forward to hearing the workgroup's feedback tomorrow. As a reminder, the charges to the work groups for this afternoon are to discuss current gaps in the field, topics or issues the work groups could help address, and specific project ideas, and also to give feedback

on the components of the RUSP Condition Nomination and Evidence Review Process discussed at today's meeting. So, I'm going to adjourn the Committee meeting for today. We will resume here tomorrow morning at 9:30.

[Whereupon, the meeting was adjourned.]