Health Resources and Services Administration

Advisory Committee on Heritable Disorders in Newborns and Children

Meeting

10:00 a.m. to 2:45 p.m.

December 1, 2020

Present

Advisory Committee Members

Cynthia M. Powell, MD (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, MD
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health
Co-Director, Newborn Screening Laboratory
Wisconsin State Laboratory of Hygiene

Kyle Brothers, MD, PhD
Endowed Chair of Pediatric Clinical and Translational Research
Associate Professor of Pediatrics
University of Louisville School of Medicine

Jane M. DeLuca, PhD, RN
Associate Professor Clemson
University School of Nursing

Shawn E. McCandless, MD
Professor, Department of Pediatrics
Head, Section of Genetics and Metabolism
University of Colorado Anschutz Medical Campus
Children's Hospital Colorado

Annamarie Saarinen
Co-founder, CEO
Newborn Foundation

Scott M. Shone, PhD, HCLD(ABB)
Director
North Carolina State Laboratory of Public Health

Designated Federal Official

Designated Federal Official
Mia Morrison, MPH
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

Ex-Officio Members

Agency for Healthcare Research & Quality
Kamila B. Mistry, PhD, MPH
Senior Advisor Child Health and Quality Improvement

Centers for Disease Control & Prevention
Carla Cuthbert, PhD
Chief, Newborn Screening and Molecular Biology Branch
Division of Laboratory Sciences
National Center for Environmental Health

Food and Drug Administration
Kellie B. Kelm, PhD
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health

National Institutes of Health
Melissa Parisi, MD, PhD
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Health Resources & Services Administration
Michael Warren, MD, MPH, FAAP
Associate Administrator,
Maternal and Child Health Bureau

Organizational Representatives

American Academy of Family Physicians
Robert Ostrander, MD
Valley View Family Practice

American Academy of Pediatrics
Debra Freedenberg, MD, PhD
Medical Director, Newborn Screening and Genetics, Community Health Improvement
Texas Department of State Health Services

American College of Medical Genetics & Genomics
Maximilian Muenke, MD, FACMG
Chief Executive Officer

American College of Obstetricians & Gynecologists
Steven J. Ralston, MD, MPH
Chair, OB/GYN
Pennsylvania Hospital

Association of Maternal & Child Health Programs
Jed L. Miller, MD, MPH
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, PhD
Manager, Laboratory Operations Unit
Texas Department of State Health Services

Association of State & Territorial Health Officials
Christopher Kus, MD, MPH
Associate Medical Director
Division of Family Health
New York State Department of Health

Association of Women's Health, Obstetric & Neonatal Nurses
Jacqueline Rychnovsky, PhD, RN, CPNP, FAANP
Vice President, Research, Policy and Strategic Initiatives

Child Neurology Society
Jennifer M. Kwon, MD, MPH, 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
Jacob Hogue, MD
Lieutenant Colonel, Medical Corps, US Army
Chief, Genetics, Madigan Army Medical Center

Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development

March of Dimes
Siobhan Dolan, MD, MPH
Professor and Vice Chair for Research Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine and Montefiore Medical Center

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

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Procedings

>> CYNTHIA POWELL: All right. Thank you. Welcome, everyone. Welcome to the December 2020 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children. I'm Dr. Cynthia Powell, the committee Chair. To start the meeting, we will begin by taking roll followed by a few items of committee business.

All right. For the roll, representing the Agency for Healthcare Research and Quality, Kamila Mistry.

>> KAMILA MISTRY: Here.

>> CYNTHIA POWELL: Mei Baker.

>> MEI BAKER: Here.

>> CYNTHIA POWELL: Kyle Brothers.

>> KYLE BROTHERS: Here.

>> CYNTHIA POWELL: Jane DeLuca. I saw you earlier, Jane. You're muted. I see. She's waiving her hand. Okay. From the CDC, Carla Cuthbert.

>> CARLA CUTHBERT: Here.

>> CYNTHIA POWELL: From FDA, Kellie Kelm.

>> KELLIE KELM: Here.

>> CYTHNIA Powell: From HRSA, Michael Warren.

>> MICHAEL WARREN: Here.

>> CYNTHIA POWELL: Committee member Shawn McCandless.

>> SHAWN MCCANDLESS: Here.

>> CYNTHIA POWELL: NIH, Melissa Parisi.

>> MELISSA PARISI: Here.

>> CYNTHIA POWELL: I'm here. Committee member Annamarie Saarinen.

>> ANNAMARIE SAARINEN: Here.

>> CYNTHIA POWELL: Committee member Scott Shone.

>> SCOTT SHONE: Here.

>> CYNTHIA POWELL: Now for the organizational representatives. From the American Academy of Family Physicians, Robert Ostrander.

>> ROBERT OSTRANDER: Here.

>> CYNTHIA POWELL: From the AAP, Debra Freedenberg.

>> DEBRA FREEDENBERG: Here.

>> CYNTHIA POWELL: From the American College of Medical Genetics, Max Muenke.

>> MAX MUENKE: I'm here.

>> CYNTHIA POWELL: From the American College of Obstetricians and Gynecologists, Stephen Ralston. From the Association of Maternal and Child Health Programs, Jed Miller. From the Association of Public Health Laboratories, Susan Tanksley.

>> SUSAN TANKSLEY: Here.

>> CYNTHIA POWELL: From the Association of State and Territorial Health Officials, Chris Kus. From the Association of Women's Health and Obstetric and Neonatal Nurses, Shakira Henderson.

>> SHIKRA HENDERSON: Here.

>> CYNTHIA POWELL: Child Neurology Society, Jennifer Kwan.

>> JENNIFER KWAN: Here.

>> CYNTHIA POWELL: Department of Defense, Jacob Hogue.

>> JACOB HOGUE: Here.

>> CYNTHIA POWELL: From the Genetic Alliance, Natasha Bonhomme?

>> NATASHA BONHOMME: Here.

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

>> SIOBHAN DOLAN: Here.

>> CYNTHIA POWELL: Cate Walsh Vockley from the NSGC will not be able to join us today due to clinic responsibilities. From the Society for Inherited Metabolic Disorders, Georgianne Arnold.

Okay. All right. Now, I'm going to turn things over to our DFO, Mia Morrison.

>> MIA MORRISON: Thank you, Dr. Powell. PSA, could you advance to the next slide? Next. Next. Thank you.

So I have standard reminders to the committee that I would like to go over. I want to remind the committee members that as a committee we are advisory to the Secretary of Health and Human Services, not to the Congress. Go back one slide, please. Thank you. For anyone associated with the committee or due to your membership on the committee, if you receive inquiries, please let Dr. Powell and I know prior to committing to an interview about the committee. I also must remind committee members that you must recuse yourself from participation in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner, unless you are also an

employee of the organization or unless you have received a waiver from HHS authorizing you to participate. When a vote is scheduled or an activity is proposed and you have a question about a potential conflict of interest, please notify me immediately. Next slide, please.

So according to FACA, all committee meetings are open to the public. If the public wished to participate in the discussion, the procedures for doing so are published in the federal register and/or announced at the opening of the meeting. For this particular meeting, we said that there would be a period of public comment. Only with advanced approval of the Chair or the DFO, public participants may question committee members or other presenters. Public participants may submit written statements. Also, public participants should be advised that committee members are given copies of all written statements submitted to the public, and we do state this in the FRN as well as the registration website. Any further public participation will be solely at the discretion of the Chair or the DFO. Are there any questions? Okay. Thank you.

And Dr. Powell, I'll turn it back over to you.

>> CYNTHIA POWELL: Thank you, Mia.

Before we begin today's presentations and discussions, the committee has several items to address. First of all, I'd like to announce that Dr. Shakira Henderson will be replacing Dr. Jacqueline Rychnovsky as the new organizational representative from the Association of Women's Health, Obstetric, and Neonatal Nurses, or AWHONN. Dr. Henderson is a hospital-based nurse researcher, health educator, certified neonatal nurse, and founder and senior system administrator of the Vitant Health Center for Research and Grants in North Carolina. She will be assuming the role of Vice President Research Officer at UNC Health in December 2020. Dr. Henderson holds dual doctoral degrees, Ph.D. and DNP, as well as master's degrees in public health, anatomical sciences, and advanced nursing practice with a sub-specialization in nursing education.

Dr. Henderson's expertise in the innovative application of research and nursing practice to increase generation of research from the bedside and expedite translation of evidence into practice is reflected in her receipt of numerous regional, state, and national awards for leadership, teaching excellence, public health advocacy, nursing practice, mentorship, and innovation. Dr. Henderson serves as an elected member and neonatal expert on the National Board of the Association of Women's Health, Obstetric, and Neonatal Nurses. We are very excited to welcome you, Dr. Henderson. Thank you to Dr. Rychnovsky for your service to the committee.

Next, as noted at the August 2020 meeting, the committee received a nomination package for MPS II, Hunter syndrome. HRSA is in the process of conducting the initial review and we will keep the committee apprised of next steps.

Due to an administrative correction, as a matter of procedure, the committee must revote on the September 2019 minutes. Committee members and organizational representatives received a draft of the September 2019 minutes to review. We received no new edits. Are there any additions or corrections before we vote? All right. Hearing none, we'll proceed to asking the voting members of the committee to state whether they vote yes, no, or abstain. Mei Baker.

>> Mei BAKER: Yes.

>> CYNTHIA POWELL: Kyle Brothers.

>> KYLE BROTHERS: Yes.

>> CYNTHIA POWELL: Carla Cuthbert.

>> CARLA CUTHBERT: Yes.

>> CYNTHIA POWELL: Jane DeLuca.

>> JANE DELUCA: Yes.

>> CYNTHIA POWELL: Kellie Kelm.

>> KELLIE KELM: Yes.

>> CYNTHIA POWELL: Shawn McCandless. Since you were not present for that meeting, Shawn, we have you abstaining. Kamila Mistry.

>> KAMILA MISTRY: Yes.

>> CYNTHIA POWELL: Melissa Parisi.

>> MELISSA PARISI: Yes.

>> CYNTHIA POWELL: I vote yes. Annamarie Saarinen.

>> ANNAMARIE SAARINEN: Yes.

>> CYNTHIA POWELL: Scott Shone.

>> SCOTT SHOWN: Yes.

>> CYNTHIA POWELL: Michael Warren?

>> MICHAEL WARREN: Yes.

>> CYNTHIA POWELL: All right. Receiving all yeses from those members present and able to vote, those minutes have been approved.

All right. Next, the committee members and organizational representatives received a draft of the August 2020 minutes to review. HRSA incorporated the edits we received and disseminated an updated version to the committee. Are there any additions or corrections before we vote on the August 2020 minutes? All right. Hearing none, we'll go ahead and ask the eligible committee members to vote for approval of the August 2020 minutes. Mei Baker.

>> MEI BAKER: Yes.

>> CYNTHIA POWELL: Kyle Brothers.

>> KYLE BROTHERS: Yes.

>> CYNTHIA POWELL: Carla Cuthbert.

>> CARLA CUTHBERT: Yes.

>> CYNTHIA POWELL: Jane DeLuca.

>> JANE DELUCA: Yes.

>> CYNTHIA POWELL: Kellie Kelm was not present at that meeting, so we have you abstaining, Kellie. Shawn McCandless.

>> SHAWN MCCANDLESS: Yes.

>> CYNTHIA POWELL: Kamila Mistry.

>> KAMILA MISTRY: Yes.

>> CYNTHIA POWELL: Melissa Parisi.

>> MELISSA PARISI: Yes.

>> CYNTHIA POWELL: I vote yes. Annamarie Saarinen.

>> ANNAMARIE SAARINEN: Yes.

>> CYNTHIA POWELL: Scott Shone.

>> SCOTT SHONE: Yes.

>> CYNTHIA POWELL: Michael Warren.

>> MICHAEL WARREN: Yes.

>> CYNTHIA POWELL: All right. Those minutes are approved. Thank you all.

In August, the committee received presentations on two reports, assessing values as part of the newborn screening committee's evidence review process and the review of newborn screening timeliness. Dr. Kemper and Lam have incorporated feedback from the discussions into both reports and committee members were provided with final drafts in the briefing book.

So, for today, our meeting topics are as follows: First, the committee will vote on whether or not to approve the final report on the review of newborn screening implementation for spinal muscular atrophy. Next, Dr. Kemper will give a presentation on newborn screening decision-making criteria and the decision matrix. After Dr. Kemper's presentation, I'll lead a committee discussion on ways to update the current decision matrix.

The committee received three requests for public comment. Dylan Simon from the EveryLife Foundation will provide an update on the second newborn screening bootcamp. Stephen Holland will discuss newborn screening for mucopolysaccharidosis and mucolipidosis. And finally, Ryan Colburn will provide a statement in support of expanding access to deidentified newborn screening data to accelerate research for Pompe and other rare diseases.

In the afternoon, Dr. Kemper will present on the review of newborn screening implementation for added RUSP conditions, SCID, Critical Congenital Heart Disease, Pompe disease, MPS I, and X-linked adrenoleukodystrophy. For our last presentation, we'll hear from a panel on the newborn screening in genomic medicine and public health program.

I'll now turn it back over to Mia who will provide guidance for participating on the webinar. Mia.

>> MIA MORRISON: Thank you, Dr. Powell. Next slide, please.

So for members of the public, audio will come through your speakers, so please make sure to have your computer speakers turned on. If you can't access audio through the computer, you may dial into the meeting using the telephone number in the e-mail with your Zoom link. This meeting will not have a chat feature, but we do have the public comment period scheduled later today. For committee members and organizational representatives, audio will come from your computer as well. And you will be able to speak using your computer microphone. If you can't access the audio microphone through your computer, you may need to dial into the meeting also using the telephone number in the e-mail with your user-specific Zoom link. Please speak clearly and remember to state your first and last name to ensure proper recording for the committee transcript and minutes. The chair will call on committee members and then organizational representatives. In order to better facilitate the discussion, committee members and org reps should use the raise hand feature when you would like to make comments or ask questions. You may find the raised hand feature by clicking on the participant icon and choosing raise hand. Please note that depending on your device or operating system, the raise hand feature may be in a different location. To troubleshoot, please consult the webinar instructions in your briefing book.

Thank you, Dr. Powell. I'll turn it back over to you.

>> CYNTHIA POWELL: Thank you.

First on our agenda, the committee will vote on whether or not to approve the review of newborn screening implementation for spinal muscular atrophy final report. If the committee votes to approve, I will submit the report to the Secretary on behalf of the committee and the report will be posted to the committee website.

As you may recall, in February 2018, the committee voted to recommend to the Secretary of Health and Human Services to expand the RUSP to include the addition of SMA due to homozygous deletion of exon 7 in survivor motor neuron 1. In July 2018, the committee was notified that the Secretary had accepted the committee's recommendation and requested the report, quote, describing the status of implementing newborn screening for SMA in clinical outcomes of early treatment, including any potential harms for infants diagnosed with SMA. In collaboration with subject matter experts, Dr. Kemper, Dr. Reem, and Dr. Lam have developed a report detailing states' experiences with implementation of screening for SMA and its impact on newborns who are diagnosed with the condition. In August, the committee received a presentation from Dr. Kemper and reviewed the report.

Since then, feedback from committee members and organizational representatives has been incorporated and a final draft was included in the December briefing book. Thank you to all who provided input on the revised draft. The final version includes the following substantive changes: In August of 2020, Risdiplam was approved to treat adults and children with SMA2 -- with SMA who are two months of age and older. The report now clarifies that testing for SMN2 copy number requires a separate assay. And assessing for SMN2 copy numbers was pulled into its own subsection within the report and additional details were added, including that at least some newborn screening programs are using a droplet digital PCR method report to report SMN2 copy number.

Dr. Kemper and I will now take any questions or comments from committee members. But before I open the floor for questions, I'd like to introduce Dr. Kemper. Alex Kemper is the Division Chief of Ambulatory Pediatrics at Nationwide Children's Hospital and Professor of Pediatrics at the Ohio State University College of Medicine. He completed his pediatric

residency training at Duke University followed by combined fellowship training in health services research and medical informatics with residency training in preventative medicine at the University of North Carolina. Dr. Kemper served as a member of the U.S. Preventative Services Task Force from 2014 through 2018. In 2011, Dr. Kemper joined the executive editorial board of the Journal of Pediatrics and developed a new section of the Journal focusing on quality improvement. In 2013, he was appointed Deputy Editor of Pediatrics.

All right. So now I'll open it up for committee discussion. First, we'll take committee member comments first followed by those from organizational representatives. As a reminder, please use the raise hand feature. I'll call on you in order of when you raised your hand. I'm sorry if I don't get all of these in order. I see Scott Shone.

>> SCOTT SHONE: Hi, Dr. Powell. I apologize for missing this on the first review and seeing it over the holiday reading. I would like to request a small tweak to the summary, the first paragraph in the summary of conclusions. It currently states SMA screening does not require new equipment or expertise. That actually contradicts with page 11, which says requires little to no additional equipment or expertise. I think it should match that. Because reality is, a lot of newborn screening programs and laboratories have had to upgrade their SCID equipment to accommodate the addition of SMA, and I fear that saying it does not require new equipment will tie the hands of programs who have yet to add or who are currently advocating to add and requesting potential funds for equipment. So I would like that sentence to be revised to say SMA screening requires little to no additional equipment to reflect that there are some needs that need to be addressed in our programs around the country.

>> CYNTHIA POWELL: Okay. Thank you. Thank you for catching that. All right. Any other comments from committee members? If not, we'll open it up to organizational representatives. All right. I'm not seeing any. Okay. We'll go through requesting the members of the committee to vote to whether or not to approve this or abstain the final report for the SMA. All right. Do I have a motion to approve the report first?

>> SHAWN MCCANDLESS: I move to accept the report. This is Shawn McCandless.

>> CYNTHIA POWELL: All right. Thank you. Is there a second?

>> KAMILA MISTRY: I second. This is Kamila Mistry.

>> CYNTHIA POWELL: All right. Now we'll go through the roster whether or not to vote for approval or abstain. Mei Baker?

>> MEI BAKER: Approve.

>> CYNTHIA POWELL: Kyle Brothers.

>> KYLE BROTHERS: Approve.

>> CYNTHIA POWELL: Carla Cuthbert.

>> CARLA CUTHBERT: Approve.

>> CYNTHIA POWELL: Jane DeLuca.

>> JANE DELUCA: Approve.

>> CYNTHIA POWELL: Kellie Kelm.

>> KELLIE KELM: Approve.

>> CYNTHIA POWELL: Shawn McCandless.

>> SHAWN MCCANDLESS: Approve.

>> CYNTHIA POWELL: Kamila Mistry.

>> KAMILA MISTRY: Approve.

>> CYNTHIA POWELL: Melissa Parisi.

>> MELISSA PARISI: Approve.

>> CYNTHIA POWELL: I approve. Annamarie Saarinen.

>> ANNAMARIE SAARINEN: Approve.

>> CYNTHIA POWELL: Scott Shone.

>> SCOTT SHONE: Approve.

>> CYNTHIA POWELL: And Michael Warren.

>> MICHAEL WARREN: Approve.

>> CYNTHIA POWELL: All right. The committee has voted to approve the SMA report with the change mentioned by Dr. Shone.

Our next presentation is a continuation of the committee's work to review the condition nomination, evidence review, and decision-making processes.

In August, Dr. Kemper presented an overview of the analysis of the evidence review process and strategies to better inform the committee's deliberations and decisions, including methodologies and strategies for assessing stakeholder values and preferences in newborn screening decision-making.

Today, Dr. Kemper will present on newborn screening decision-making criteria and the matrix. Afterwards, we'll have a discussion. As you listen to Dr. Kemper's presentation, please keep the following questions in mind: Are there components of the decision matrix that need clarification? How should the committee approach a B rating should the matrix include additional guidance? Should cost data be considered as part of state readiness or feasibility? If so, what cost data could be included? If a condition were to be removed, how would the matrix be used in that process?

Dr. Kemper, the floor is yours.

>> ALEX KEMPER: Thank you very much, Dr. Powell.

So I'm going to frame the presentation about the decision matrix with just a couple of observations. The first is that making decisions about which things to recommend for the -- to be included in the RUSP is challenging. There are a lot of complex issues that need to be considered. Later this afternoon, I'm going be recapping a prior presentation about what we

have learned after things have been added to the RUSP. I think it's important to recognize what a tremendous success this work has been. But, again, making these decisions about which things to recommend for the RUSP is really quite challenging.

The fact that the committee is taking a detailed look again at the matrix doesn't mean that the matrix itself doesn't work. But I think that it's important as any group moves forward to continue to look back at its processes. I've served on many other evidence review committees and what I've learned is that this kind of critical appraisal is really important, but the fact that one needs to take a critical look at how decisions are made does not mean that any of the prior decisions have been wrong. It just reflects how complicated these issues are and how there's always opportunity to clarify the decision-making process. So I'm really happy that the advisory committee has decided to continue to look at this again.

What I'm going to do over the next little bit is just to recap the history of the matrix and how it's been used and really tee things up for Dr. Powell to lead a conversation about the matrix. Certainly, this is not the first conversation about the matrix. It's not the last conversation about the matrix. I think that there's just tremendous value in doing this. I really appreciate this opportunity. Next slide, please.

So, again, the objectives today are for this talk to talk about the development and use of the decision matrix and really guide where the advisory committee would like changes in the matrix. Next slide.

So there was a report that was published back in 2014, you know, which seems like several lifetimes ago now, in genetics and medicine that outlined the decision matrix as it stands now. I'd refer back to anybody who wants more detailed information about how the matrix was developed to look at this report. Next slide, please.

So this is the decision matrix. It's complex. Again, I think that reflects the complexity of the decision-making process. The first step, and I should say that everything is really developed to help inform the decision matrix from the nomination process through the various components of the evidence review, leading up to the discussion around where a condition might fall in the matrix. We will continue to refine our approach to match whatever future iterations of the decision matrix looks like. I wanted to put it out there that, really, our job in the evidence review process is to tee things up to make it easier for the deliberations that have to happen around the decision matrix.

So the first step in the way to think about this is the systematic review of the evidence that allows the advisory committee to debate about issues related to the net benefit of screening on outcomes. And the net benefit can be classified into a significant benefit. So where it's clear that the benefits outweigh the harms, it could be small to zero. So things could be evenly weighed. It could be negative, meaning that the potential harms really outweigh the benefits, or the evidence could be so uncertain that you can't judge whether or not there's a degree to which there is a net benefit. So along with determining whether or not there is the degree of benefits and harms, there's issues of the certainty of the evidence. So how clear is the evidence? Are there questions about whether or not new studies might actually change the degree to which you think that there is the relative balance of benefit and harm?

The next step then is related to the readiness of newborn screening programs to implement the condition and screening for the condition and the feasibility as well. And so, as you can see on the slide, readiness could be considered, you know, prime time, ready to go, developmental, meaning more time and resources are needed to get going, or programs could be unprepared. At the same time, the advisory committee has debated issues of readiness, issues of feasibility have come into play, which we have teased out into high or moderate

versus low. You can see how, depending upon where you think the advisory committee places the net benefit and certainty and readiness and feasibility, you can end up in one of these boxes that can help guide the future decisions. If the evidence is moderated or the advisory committee deems benefits to be small to zero or negative, you can see that the issues of readiness and feasibility at the -- within the newborn screening programs is of less relevance. Again, all these things are tied to letters and numbers to help with the communication. Next slide, please.

So again, there are some observations that I wanted to make based on prior experience with this. So there's always going to be uncertainty. It's just the nature of issues of newborn screening that there's always going be some degree of uncertainty. Next slide, please.

There is this sentence in the publication that I'd like to read. A B rating of the evidence indicates moderate certainty that screening would lead to a significant net benefit. The term moderate indicates that the advisory committee believes that further research could change the magnitude or direction of findings such that the assessment of net benefit would be small to zero or negative. So in the original publication, the thing that separates an A from a B is tied to whether or not, you know, the evidence might flip based on -- might flip related to net benefit based on future research. Next slide, please.

So in that document, we stated that A1 or A2 would lead to recommendation to the RUSP, and A3 or A4, again, this gets to the degree to which newborn screening programs are ready to implement things or issues of feasibility, would be at the discretion of the advisory committee, and the B, C, D, or L wouldn't be recommended to the RUSP, that the advisory committee would then provide guidance regarding research needs. Now, again, remember that this document was put together in 2014, and since then there has been a lot of experience with the -- with using the matrix. So I'm going to talk to you about where conditions have fallen off. Just because there's been a deviation from the report that was written before there was experience with it, again, doesn't mean that the matrix itself doesn't work. It just means that this is a natural evolution in the process. Next slide, please.

So this slide lists the decision matrix and the subsequent recommendations along with where the consensus was in terms of where the condition was on the matrix and then the recommendations to the RUSP, along with the vote by the advisory committee. I won't read this whole thing, but I'll leave it up there for a second so you can look at it. But I'd like to point out that there have been some conditions that the advisory committee placed in the B category that were ultimately recommended to the advisory committee and preceded the use of the decision matrix. I'll let you look at that for one second before moving on. Next slide, please.

Before I turn things back over to Dr. Powell, I just want to point out that refining these kinds of processes is normal and expected. And so just to help frame this again, these are a picture of Darwin's finches from the Galapagos, each of which has over millennia become uniquely situated to its particular environment. When we first put together the matrix, a lot of this was adopted from the process used by the US Preventative Services Task Force, and I think it's been helpful, but I also think that we're, like Darwin's finches, going to continue to evolve. And I think that the conversation we're about to have is going to be really, really helpful in thinking through this process. And I strongly suspect that this will lead to changes in the matrix. You know, at some future time, not too along from now, we'll be revisiting this again and continuing to refine this again. This is a natural and good and expected process.

So with that, I'll hand things back over to Dr. Powell.

>> CYNTHIA POWELL: Thank you, Dr. Kemper.

So I'd like to use the remaining time to explore if there are any ways to strengthen the decision matrix. Again, here are a few specific questions I'd like to pose for your consideration. Are there components of the matrix that need clarification? How should the committee approach a B rating? Should the matrix include additional guidance? Should cost data be considered as part of state readiness or feasibility? If so, what cost data could be included? If a condition were to be removed, how would the matrix be used in that process?

So first, we'll take questions or comments from the committee members followed by the organizational representatives. Please raise your hand. Okay. Not seeing any from committee members at this time, so first Dr. Ostrander.

>> DR. OSTRANDER: Looking this over, I wonder if -- and I think this is part of this evolution thing that Alex mentioned -- I wonder if we should have a more scaler representation of certainty as opposed to just high, moderate, and low, and if that wouldn't help with some of these B things as opposed to just those three boxes. I would suggest that that might be considered. The scaler for some of the other things, I don't feel as strongly about that in terms of the readiness and preparedness and so on and so forth. But I think some of the certainty stuff would be helpful if it were more scaler because it would help with these nuanced decisions when things are right on the cusp, especially with those, as you said, with those B ratings. There's always going to be a subtext during the conversation as to what's affecting that rating, but that would be my one thought.

A condition would be removed. I think the matrix could easily be incorporated very much the way it is, perhaps with a scaler for the high, moderate, and low net benefit for removing things. And I just think we should have -- we should implement a process as a committee about when to investigate things. I mean, would we nominate things to be removed because a bunch of experts in our group are beginning to question it? Should we periodically have a subgroup that reviews things and sees if anything more than five years out or ten years out should be sunsetted? That's how we do things in medical center with all their policies is, every ten years, there is a small group that looks and at least comments about whether something should be sunsetted. I do think we should have a process that's organized as opposed to just ad hoc looking at things that maybe we could pull it off the panel. Those are my two comments.

>> CYNTHIA POWELL: Thank you. All right. Next, Jed Miller?

>> JED MILLER: Yes, hello. This is Jed Miller, Association of Maternal and Child Health Programs. My comment is somewhat related to what Dr. Ostrander said in that just wondering if the concept of net benefit needs any clarification, you know, or potential expansion. I don't mean to overly formalize it. But I think there might be a tendency to think about net benefit in somewhat of a unidimensional fashion where it's either there's an arrow up or an arrow down perhaps and where is the balance there. I'm just wondering if there's any -- from Dr. Kemper or anybody, any thoughts about if those net -- if the benefits, you know, versus the risks are skewed towards different populations, for instance, if, you know, based on, say, race, ethnicity, geography, and other such factors, wondering if there are disparities there, how do we handle that, and acknowledging that maybe the research is not mature enough to be able to discern that. I'm just wondering if there are any thoughts about -- I'm wondering whether or not just that concept of net benefit and thinking about how granular we're able to, you know, appreciate what's going on is. And I was wondering if that might be helpful, including for cases where it's borderline. Thank you.

>> CYNTHIA POWELL: Thank you. Natasha Bonhomme.

>> NATASHA BONHOMME: Good morning. Thank you. Natasha Bonhomme with Genetic Alliance. I have a couple of comments that relate to some things that have been said.

So one is I agree. I think really determining are there phrases in this work that we need to go back and make sure that everyone has the same definition or is working from that same definition, particularly net benefits as was just discussed as that is something that is looked and perceived at differently, depending which stakeholders you are involving in that discussion. So that's one point.

My second point is for question number four about removing conditions. I think that may warrant a separate conversation to determine what would that process be, what would need to go into that process, and then determine, okay, does this matrix fit or would the committee need to create something different? So, for me, it's a little bit hard to answer that question without really exploring what would that mean to remove a condition? And how feasible is that since I don't think we've had a lot of conversation openly about that in a very tangible way.

And then, lastly, and I don't think anyone will be surprised hearing me say this, is I hope that after or parallel to these discussions about the matrix and how it can or could be clarified, that then we also really clarify how that information is communicated out to the public. Oftentimes, the questions that I get from patient advocacy groups and even industry representatives and anyone who is trying to get into newborn screening and understand what's going on is really, okay, so how closely does the committee stick to that matrix? What are the -- how many conditions that have been recommended and added to the RUSP have gotten an A1 compared to an A2? You know, that kind of information in terms of the -- how the matrix has been applied and useful. So I think if down the line we can think about if we clarify anything that needs to be clarified through this process, how we will communicate that out to the different stakeholders that are interested.

And kind of to go along with that, to also have really a clear sense of all the different roles of people who are part of this. So I think it was the last meeting or maybe the meeting before that, Dr. Kemper did a great job kind of saying where he saw his role in all of this, and his team's role. I'm not saying that has to be set in stone or not, but I thought that was very helpful. Again, thinking how do we get that information really out there? I don't know if that's through the website or what. I don't think -- I think there are plenty of people who can think about that. But just wanted to make sure that the discussion leads to clarification and communication out to the public and the screening stakeholders.

>> ALEX KEMPER: If I could just jump in there. There are two really interesting themes that are important that I just want to make sure don't get lost. One of them is this issue of net benefit. It would be helpful for us to be able to address better, I think, in that the benefits and harms occur to different people. Right? Harms and false positives versus the infants that are going to benefit from early detection. And I think that there is an opportunity for us to think through that more and I think that's a theme that's come up in all the comments.

And then the other thing is related to the degree to which the advisory committee thinks that the matrix should be prescriptive. If you end up in a certain box in whatever the matrix might look like in the future, does that directly translate to what the advisory committee recommends where the advisory committee ends up on a matrix, just a tool to use for deliberation, a deliberation tool versus a prescriptive sort of thing.

>> CYNTHIA POWELL: Mei Baker.

>> MEI BAKER: Hi. This is Mei Baker, community member. My comment is actually followed up with the discussion and more emphasis before. Generally speaking, I would think the principle should be the same in terms of adding on or remove. The remove, the reason is because over the course you learn the things evolve. Things you didn't know, now you know. So

I was thinking in terms of review, the logistical, yes, we need to develop new one, but I would say both regular review, like every five or ten years, so you don't miss anything. Sometimes I think should allow ad hoc, too. The reason is if certain things screening do harm, you don't want to wait the scheduled time. Also, I think we need just like a nomination condition. Almost everybody should be able to nominate a condition be removed, but the important thing is that you have a process, you have evidence. I think that's, to me, I think I really like the idea of the conditions, if feasible, every five or so years we should review. For example, if you look at that SMA was defined as a B2. I'm just curious if we do today, is it still B2? I think the things evolve. We should allow ourselves to learn more and update what have we learned and recording that should be good practice.

>> CYNTHIA POWELL: Melissa Parisi.

>> MELISSA PARISI: Thank you. This is Melissa Parisi from NIH. And just to follow on, I think, both what Alex was talking about and Mei, I think the matrix, and this is my opinion and others may not share it, I think the matrix should not be prescriptive, but should really provide some general guidance. And the reasons for my saying that are really twofold. One of them is that I'm not sure we are really that great at predicting the relative success of screening when we are doing the evidence review process. I mean, I think we do the best we can. Obviously, it's very carefully considered, and the process is very rigorous. But if you look at that table that Mei was just referring to, I guess it's two slides prior to this one, and in particular, you know, we're not terribly enthusiastic if you look at the matrix rating for SMA of a B2. And, in fact, I think most people would agree that that has been a successful screening approach. And I think one of the reasons for it getting a B2 ranking, in part, was related to the timing of the evidence review and the fact that much of the supportive evidence was in the process of being published but was included in some abstracts at various meetings. You know, I think that that made people uncomfortable because it didn't have the weight of having undergone a rigorous peer review process.

That leads me to my second point. I think given the timelines that we're working under for considering conditions, I think a lot of the data are likely to fall into more of a moderate type range, a B category range in the future, and I think that's going lead to some intrinsic uncertainty. At some level, the committee has to weigh whether they feel that the general evidence of the general likelihood of benefit from the evidence as available is unlikely to be overturned or to be reversed such that they feel comfortable with recommending a condition be added to the RUSP.

So, for those reasons, I really think that the matrix is incredibly valuable, but I'd hate for it to be completely prescriptive as originally designed because I think that there is so much fluidity to some of these decisions and the strength of the evidence is somewhat variable depending on the timing of when we're reviewing it.

>> CYNTHIA POWELL: Thank you. Carla Cuthbert.

>> CARLA CUTHBERT: Thank you so much. This is Carla Cuthbert here. Please excuse me if I'm repeating myself if I didn't hear some of the comments. My internet is a little dodgy. I just wanted to, again, I really support a lot of what has been said previously. And when some of our CDC folks got together, I think that we had -- we would just like to support two points or so. Again, I think in agreeing with Melissa, we're going to be struggling more so with the B category. I think the A category, when we look at it, to some extent we'll know it. We'll see it. I don't know that that would be a whole lot of -- I don't want to say discussion, but that would not be a problem area. We're really going to be struggling a whole lot with the B category.

So we were wondering whether or not there would be benefit in sort of expanding the B

section. I know that you've expanded the A section of the matrix, but I think that there would be benefits to actually making some of these sections a little bit more explicit so that we really see and understand and have a better idea of when you were talking about that evolution process, Alex. I think that we really do need to have that broken out a little bit more so that we can really see what we're wrestling with, so that when we take another look at this in another few years, we would be able to say we have moved forward from that discussion and so on. So that was one of the things that we thought about.

I think on the addressing question four, because I think that this goes hand in hand, and I know that when we think about something being removed, it always feels as if there's a huge negative connotation. I remember some of our states saying, hey, if we add something to the RUSP in our state, it's going to be super difficult to remove it in any consequence. So we were thinking more along the lines of what, I think Mei mentioned this as well, having a periodic review, where it is an expectation that we're going to take another look at a number of these conditions. We want to be able to clean up our perspective or what we think of the RUSP. There may be conditions that maybe don't bear as much evidence anymore on being on the RUSP. Perhaps there are some secondary conditions that we may have more evidence right now that could move up to being a primary and vice versa. So I think that, perhaps, if we name it differently and just indicate that it is a periodic review, it's something that we're doing, we've been doing this for many years now, let's take a look at refining how -- what we're doing. Call it by a slightly different name and reassess much of this information. Again, we can take a look at the different types of hemoglobinopathies and all these other things and decide whether or not we need to classify them a little differently and so on. I think it bears in mind just noting that and making it just part of our regular process where, again, I don't want to speak for HRSA here, but maybe we should have an annual review of a specific condition or two and just see where we are, get some information of where we are, and have that be built into our process. Thank you. That's not all we discussed, but I think I'll stop now.

>> CYNTHIA POWELL: Scott Shone?

>> SCOTT SHONE: Indulge me for a second. This might be a little rambling because I just started thinking about responding to colleagues who have commented so far. I agree with Melissa and Carla around the B section and the challenges ahead, and the quote, the easy stuff has been done. We're finding that what was previously thought to be easy now presents some continuing ongoing challenges. But I really do -- I have great concerns, and I think we're seeing this in several of the disorders that either were in the B category, or if we went back and looked, it might have been in the B when they were initially reviewed, is that we've transitioned and Beth Tarini and Aaron Goldberg and I talked a lot about this over time is newborn screening was thought to sort of address the diagnostic odyssey, but we tend to be creating some sort of treatment or prognostic odyssey now of where do we go with these more complex disorders? I think you see it in the SMA report. I don't disagree that there is more data now, but there are even more questions. Now we're asking about we're seeing clinical labs are having challenges accurately coming up with SMN2 and we have states that have added it and still have trouble finding or having access to care. And so I guess there are even bigger questions and I think the matrix and the public health systems impact currently gets at that are going to impact these conditions that fall in that B section. I don't have a great idea on where to go with this, but, again, to give credit to colleagues, Stan Berberich and I have talked about in an e-mail going from just a screening test and a treatment to this whole system and what's in place to answer some of the questions. And perhaps if there was that, and I know there's some really great policies going on, one in our state and New York and others that we have heard about, to ask some of these questions, to look at some of the ethics of this, and wonder if we need to be -- we really need to change our thinking now around how we address these questions, multiple disorder implementations and things like that. I don't know if that was for me, but I'll stop there.

>> CYNTHIA POWELL: Thank you. Annamarie Saarinen.

>> ANNAMARIE SAARINEN: Hi. I wanted to pretty much echo everything Carla just said about taking a thoughtful approach to review. I don't know if there can be some thought given to how to systemize that a bit based on -- I know it would be so hard to do, like, hey, let's just review everything on there, but picking, you know, one or two if we were to do it that way, what are -- what are the criteria for choosing those? Is it at a certain point since implementation? Is it at a certain point since it's been ever previously looked at, that sort of thing? I feel like Dr. Kemper and his team would do a great job at sort of providing some recommendations or context around that.

And then the other thing is it's not just about, you know, is it -- if it was on the B list before, and we've got evidence that shows that it may be a candidate for review or removal, it's not a binary decision; right? Like when we have new evidence, when time passes, I think for a lot of these conditions, that review process can help inform optimization; right? I don't know that that's true for all of the conditions that are in the blood spot panel in terms of assays or things that are being improved along the way. But for things like CCHD and SMA, things like that, I absolutely think that's true, that as we have more information, when we do these sorts of reviews, there are ways to not necessarily look at should we pull this, but is there a way to improve it? Maybe we stepped into it, you know, like we're not quite there; right? But there are ways to make those sorts of improvements that the committee could participate in.

And then just from the parent perspective, I completely feel the comment on how states have said, you know, once it's there, it's really hard to pull back, and it is. There would be fallout. There would be consequences, you know. You certainly have to look at, you know, the number of children and families that have been affected positively by screening and what a removal or any substantive change to something that's been added to the RUSP looks like at the state level.

>> CYNTHIA POWELL: Thank you. Jennifer Kwon?

>> JENNIFER KWON: Hi. This is Jennifer Kwon, the organizational representative for the Child Neurology Society.

I think this has been a great discussion. I was listening to Alex's talk, thinking about the concept of net benefit. And I think Natasha brought up a great point about the multiplicity of stakeholders that are involved in determining benefit. I thought it was fascinating that SMA, which I think of as a very successful newborn screening program, got a B rating, but I also was present for those committee deliberations. And I think that the B rating reflects the really thoughtful engaged conversation about the data that they had on hand.

I also point out that X-ALD got an A raiding. And I think that, in many ways, there's a great deal of evidence to support that early diagnosis, early screening, has real benefit, not necessarily newborn screening. And so, in some ways, I think that however we review past conditions that we have approved, I don't think we should review them with an eye to whether or not they should be removed from consideration, but more with an eye to making the deliberation process more consistent over time. I think many of us recognize that committees and the committee make-up changes and how they employ the decision matrix changes. That's a good thing. It's part of the evolution of how we think about newborn screening. But it would be helpful if we had some consistent way of looking back and seeing what is the impact of that screening on states? How hard is it to identify cases? What is that -- I like Scott's term, the prognostic odyssey. What is that prognostic odyssey like for families who have a diagnosis but aren't sure what that diagnosis might mean. So I think it would be great if there was some

consistent new tool that we had to sort of review past programs in order to firm up how we think about our current matrix.

>> CYNTHIA POWELL: Thank you. Michael Warren?

>> MICHAEL WARREN: Yes. In regard to question number three, switching gears a bit about cost data, I am curious, and my understanding is that analysis looks at laboratory cost. I'm not sure what other newborn screening systems costs are included there. But, for example, if you've got a team of follow-up nurses that take those laboratory results and engage the patients and primary care providers, as new conditions are added, you sometimes reach the tipping point where you've got to bring on additional staff. So you also may need capacity if you're a state that has, for example, regional genetic centers that are relied on by your program for some of that short-term follow-up or consultation. So I don't know if those are already included. But if not, those are potential things to include.

And then, I think, getting some sense of timing from states about when those changes can be made. I think often there's the assumption that states can just raise their newborn screening fees, but sometimes there are limitations on state agencies about how often they can raise fees. That may only be able to happen once a year. It may require legislative review or governor approval or something like that. So I think getting some sense of the timing of that could be helpful as well in terms of the readiness.

>> ALEX KEMPER: Let me just respond to that to help inform the conversation. First, it's been really, really difficult to get to issues of cost. So we really do focus on trying to estimate the cost to the newborn screening program for adopting the specific laboratory test for screening. Part of it is that, you know, we're typically considering conditions that haven't been broadly implemented in newborn screening, obviously, and so the amount of information to be able to predict those other costs associated with newborn screening, so making sure that the laboratory information systems can handle things, that the right staff are there to be able to do the follow-up and to make sure the diagnostic testing is done, the cost related to long term follow-up treatment, all those kinds of things. It's such a changing and involving thing that I question our ability to do it with any degree of rigor or certainty, especially because we know that those costs, they're just going to change as people learn more. It may go up. It may go down. But I just don't want to overpromise what we can do in the evidence review process. Even the costs within the labs, there's so much variability in terms of how laboratory equipment is paid for in terms of reagent contracts versus those kinds of things. And I fully expect those things to change. I think that the best we could do is put, like, bounds, sort of upper and lower bounds, of what we think the costs are going to be. I almost imagine, like, a consumer reports filling in the circle for costs instead of the actual number. But these issues of cost are really, really difficult to get to.

>> CYNTHIA POWELL: Carla Cuthbert.

>> CARLA CUTHBERT: Thank you both to Michael and to Alex for addressing number three. And I don't know if the committee would approve Scott Grosse being able to offer some commentary on this as well. However, when we were talking about this again, we do agree that being able to factor in some cost would be helpful. I think that we could get very granular. And I don't think that would necessarily be helpful. Scott, I like what you said in terms of having upper and lower boundary. We were thinking of the nature of buckets in terms of how much generally it would cost. And we agree that at the beginning of the entire process, states would be across the board. There would be some that would be really ready to adopt. Some would have approval to be able to have money allocated to what's the process. And we hear that. But I think that when we were running through this, I think we were thinking along the lines of cost can really be an issue to implementation, especially if you're looking at a new

test that may be $20-$30, per newborn, per infant. When you're looking at costs that really fall significantly outside of what we're currently doing, I think that would be notable.

So if we're looking at something that has an exceptionally high initiating cost where, you know -- I don't want to say, God forbid, I was just thinking the possibility of using another matrix. I was mentioning to my CDC staff that that would excite me from the point of view of being a chemist, but it would be -- it would be very significant for implementation because everything we do is either at the bedside right now with point of care testing or with blood spots. Again, if we're thinking about an open mind, we need to be able to factor in how much is this going to impact us and does it really shut down the possibility of implementation. Not shut it down, but does it limit or create a really significant obstacle as we move forward? Again, this is not to say that everything is possible, but, you know, we do have NIH, HRSA, and CDC being able to provide some funds to help support implementation. So there are some dollars available. We don't want to rule it out completely. Again, I just want to make sure that we address this, but in a way that doesn't burn us out trying to get the information but acknowledges the fact that money can be an issue. So I think that's what I have to say. I don't know if Scott is able to speak to this, if you can get him permission to join in.

>> CYNTHIA POWELL: Right. I'm checking, and I'm told that we are able to let Dr. Scott Grosse comment. If we can open his microphone. As we're doing that, I would like to -- so Cate Walsh Vockley was not able to be on the meeting today, but she did submit a comment about this. As we look at newborn screening as a comprehensive system, one thing that I've always thought should be part of the matrix and part of the considerations about adding conditions is an assessment of the availability of follow-up/specialty services. I know these children will inevitably need to be seen, but if we can look critically at resources and where efforts need to be focused to improve access to care and availability of specialty provider follow-up in concert with other entities, like the American College of Medical Genetics and Genomics, I think it would add to the overall process.

>> ALEX KEMPER: Can I ask a question of the advisory committee while you're trying to get on the phone. This builds on the comments from Dr. Cuthbert and the ones you just read into the record, which is we struggle in putting together the evidence review around these notions of readiness and feasibility at the for the newborn screening laboratory program and you might argue that it's sort of an artificial split of those two concepts. And I wonder what people think about those things and whether or not they need to be more nuanced and whether or not somehow or another this issue of availability of follow-up services be incorporated into that consideration.

>> CYNTHIA POWELL: All right. Scott Grosse, you should be.

>> SCOTT GROSSE: Yes, I am. Hi. Scott Grosse, CDC. Carla did a great job of summarizing our discussion this morning, internal discussion. I also wanted to say I fully agree with what Dr. Warren said. The committee should be respectful of the budget constraints and resources constraints and timing constraints that state newborn screening programs operate under. It's really not about cost in terms of cost effectiveness. This is really about respecting state programs.

>> CYNTHIA POWELL: All right. Thank you. Robert Ostrander?

>> ROBERT OSTRANDER: Hi, AAFP organizational representative. I'm going to ask a question and I'm not advocating for one answer or the other. But should we, when we assessed net benefit, be looking at things beyond the pure biological interventions that result from newborn screening? And my comment comes partly because I've been involved in all sorts of projects over the years, which is how I got pulled into this group, that involved a lot of learning

collaboratives with partners. Part of it is because of some work that I had done with the NBA. And I think there's sometimes, honestly, some very clear benefit in having one's eyes open for early symptoms and even preemptive, non-high-tech biological interventions with some of these conditions in terms of quality of life, functional status, and so on. Again, we can come to mind over and above the potential treatments and all that, but early recognition institutional physical therapy modifications and so on. A lot of the parent partners in that organization very much would support that notion. And so is there a place with our net benefit that we should be talking about these sorts of softer interventions and benefits that come from early detection.

>> CYNTHIA POWELL: Thank you. Shawn McCandless.

>> SHAWN MCCANDLESS: Thank you, Cindy. This is Shawn McCandless. I'm a member of the committee. I'd like to respond to a couple of the points that have been raised. The first is one of the more recent points about the availability of resources and considering adding that to the decision-making matrix about whether to add something to the RUSP. And I think there's a bit of a chick and an egg question here. And that is that there may -- that sometimes you have to be identifying the disorder early to force health systems to create the resources to take care of the patients. If we always wait for the resources for care to be available, we may never get there. And so I think that -- I'm less concerned about are the resources available, because the reality is that if demand is there, the resources will become available, I think. That's usually how it works in our -- whatever our healthcare system is. There's no way to sort of systematically identify of force resources to be available prior to starting newborn screening. So I don't think there's -- I don't see that that should be something that we necessarily take into account.

The other thing that this whole conversation has sort of -- the question that's come to my mind through this whole conversation is that I think the decision matrix is a very nice way of thinking about the various aspects of what we need to do to make a decision what needs to be in place to make a decision. What's missing for me, though, is the underlying agreement about what are the parameters that need to be addressed to determine a benefit and determine readiness and feasibility. So it goes back to sort of the Wilson and Young criteria or whatever has replaced that in terms of our thought processes about a population-based mandatory screening program, and that is what are the -- what is the definition of benefit that we're looking for both short and long term? What is the cost that's important? What costs matter? And what matters about the resources and the availability of resources? And it seems to me that there's some fundamental work yet to be done by this committee or by others to define those things before the matrix really could be used as a prescriptive tool. In support of what other people have said, I think the lack of fundamental definitions and agreement about those more basic concepts means that this decision matrix can't be prescriptive because to make it prescriptive would just be gaming the system to sort of say here's what we -- we just need to make sure we get the right scores to get the thing that we're in favor of or supporting approved.

Finally, I want to address the question of the removal of conditions from the matrix. I think that whatever decision is made, there has to be some sort of automatic review for things for which there is not good long-term outcome data I think that it's really unfair to expect that there would be individuals or groups of individuals that would put themselves forward to nominate for the removal of a particular condition. And the bar for removal of a condition without sort of pre-existing definitions for what would lead to removal would be so high that I think it would be almost impossible to do. So I think that there needs to be either some sort of conditional approval for addition to the RUSP with a requirement for follow-up data. And I think this is a somewhat of a tangent, but I think the SMA report that we heard today is a really compelling evidence that two years not long enough, that that report, as good as it is, doesn't answer the fundamental questions about the treatment for SMA. In fact, what it does is it raises more questions about the treatment that really need to be answered. And that's not to say that

it indicates SMA shouldn't be screened. The screening program has been successful. The questions are about the long-term outcomes and the long-term net benefit. And I think that that's so -- and I think there needs to be some sort of long-term, long-range plan in place and there needs to be some sort of automatic review triggered. I'm not sure five years is even the right about of time, but there needs to be some sort of continual reassessment of the RUSP.

I've addressed a number of different issues there. And I apologize for the somewhat rambling nature of those comments.

>> CYNTHIA POWELL: No, that's fine. Thank you. And if I could ask you to just go back to your first comment regarding the resources, that we can't expect resources to be available prior to, you know, instituting screening. Are you referring to both financial resources as well as other types of resources, such as, you know, providers, specialty providers and the other components that would be needed?

>> SHAWN MCCANDLESS: I was referring more to the latter, to the availability of specialists and healthcare providers and services that needed to deliver therapies more so than the financial resources. It seems to me that the financial resources are available. They just need to be leveraged. There are ways to accomplish addressing the cost, although I don't want to minimize -- I don't want to minimize the intensity of how new therapies are increasing the cost of delivering care, but it seems to me that the bigger issue is not how to pay for it right now, at least. It's who's going to actually deliver the care and how will the care be delivered? And is there the ability to ensure that every infant screened in the United States is going to have equal -- relatively equal access to care? And my point is that if we wait for those things to be available to add new things, new conditions for screening, we probably would never be able to add anything, that we have to add them to screening to drive the process of building resources in the community.

>> CYNTHIA POWELL: Okay. Thank you. Georgianne Arnold?

>> GEORGIANNE ARNOLD: Am I unmuted?

>> CYNTHIA POWELL: Yes, we can hear you. Thank you.

>> GEORGIANNE ARNOLD: Cynthia, you kind of addressed one of the questions I had from what Shawn had said, which was workforce. The SIMD and ACMG are quite concerned about workforce. I'm sure Jennifer would talk about child neurology as well. And I don't know that increasing -- increasing the number of conditions now and waiting for the workforce to catch up is going to work well for us. And I'm wondering if this committee is interested -- if this group is sort of interested in a workforce committee that could liaison with ACMG, SIMD, child neurology, ACOG, and other societies, because I see there's plenty of money to go around, but having it spent on you, you have to become important to them. So states have money. Not a lot, but they have money if they want to spend it on us. So I think money is less of an issue at this point than workforce. And I'm very concerned about our workforce.

The other issue review in five years, I've been on some ACMG committees that try to review everything every five years. Certainly, there's too many things on the RUSP list right now for us to be reviewing them every five years. However, we could make that a condition of new ones or of some that were a lower B grade, you know, a lower grade. So if you're -- maybe there was more controversy to.

And I had one more thing, but I can't remember what it was. Thank you.

>> CYNTHIA POWELL: Sure. Thank you. Jennifer Kwon?

>> JENNIFER KWON: Hi. This is Jennifer Kwon, organizational representative for the Child Neurology Society. I actually really was intrigued by Shawn's idea of having longer-term follow-up. So looking at these programs, maybe not two years out or maybe not even five years out, but a little bit longer. Maybe we could just collect some simple information. How many infants were screened as positive? How many have we been successful in following? How many have we lost to follow-up? I don't think that -- it's not a way to judge negatively a program, but just to help us understand just on a basic level, give us a report card of how we're doing with some of these conditions. And that will almost inevitably lead to conversations about what are the barriers to follow up, and they're almost certainly workforce related, as Georgianne brought up. But I do like the idea of sort of taking a look at some of these programs. For example, Pompe disease is not a bad example. We know that early screening is valuable. Early diagnosis and treatment are valuable, but how these children do long term may be unexpected to us. So I think it would be helpful.

>> ALEX KEMPER: I just wanted to tack something on to what Dr. Kwon said. One of the great things about newborn screening is its universal availability. One of the things I'd ask the advisory committee to consider if it looks at things like Dr. Kwon just talked about is whether or not there are any unexpected disparities, you know, by region, rural/urban, by race, ethnicity, and so forth.

>> CYNTHIA POWELL: Susan Tanksley?

>> SUSAN TANKSLEY: Hi, can you hear me?

>> CYNTHIA POWELL: Yes.

>> SUSAN TANKSLEY: Susan Tanksley representing the Association of Public Health Laboratories. I first want to make a comment about cost considerations being as part of the state readiness or feasibility. I just wanted to comment. So states have -- all states have different funding mechanisms. And so some are fee based. Some are general revenue based. Some are funded a lot through Medicaid. Some programs have a lot of funds. A lot of programs have few funds. And so, you know, I think it's important to I think it was Carla who suggested having kind of buckets of relative costs. Sometimes when you get too granular on the costs and you state like, for example, I've seen that SMA costs pennies to add to a newborn screening program. But, in actuality, programs have been screening for SCID for a lot of years now, so just adding SMA may seem simple, but when you have to replace equipment, when you have more data coming out, you have more cases, so you do need additional staff for follow-up. And there's second tier testing. You know, states also use -- when disorders are added to the panel, sometimes that's an opportunity to fill gaps that have been created by lessons learned from, you know, trying to add with too few resources in the past. And so by adding really -- sometimes by having the information of, you know, this is just going to be pennies per disorder or per child screened may do more harm to the state as they attempt to get funding for the disorder and to actually improve their program to be able to do the screening that they've already been doing and add the new disorder. But I did like the bucket concept of what's the relative expense and what might -- it's important to know what sort of money may be needed by a program. But, again, it may do more harm when you get too granular with it.

I really like the idea in regard to workforce. Georgianne's comment about a workforce committee, and really looking at what's available. At some point, as we add more and more conditions, and it seems like the metabolic community is what gets hit the hardest by the conditions that we screen for, you know, at some point, do we reach a tipping point where we're going to actually harm -- do more harm because there's less access to care for everyone? I understand the need to create demand, but are we actually seeing more physicians joining,

becoming metabolic specialists and going into these specialties where we have increased demand due to newborn screening? That's all I have. Thank you.

>> CYNTHIA POWELL: Thank you. Just going back for a minute to Jennifer and Shawn who commented about the need for, perhaps, longer follow-up information, at least five, maybe up to ten years or more, do you think we're currently able to do that? Do you think the current system is able to assess that? Or what would be needed in the future if, you know, one were to try to do much longer follow-up? Shawn?

>> SHAWN MCCANDLESS: Yeah, Cindy. This is Shawn McCandless. I'm a member of the committee. That's a really great question. And I think, from my perspective, there would be two components. One would be that there will be -- I think Pompe, the example that Jennifer Kwon brought up, is a really good example. Over time, there's been a growing body of literature that suggests that there were unexpected outcomes, and that the natural history of the disorder has significantly changed with therapy for the better in many ways, but also unmasking some unexpected aspects of the natural history that we just didn't see because patients didn't survive long enough. So I think there will be a growing body of literature that will support the facts about the physical benefits to patients that are receiving these treatments after early diagnosis. There would also be, I would expect, a growing body of literature supporting the timing of the initiation of the therapy that would suggest that earlier treatment is better and may even raise questions about whether prenatal treatment is needed in some cases. And I think SMA is one condition where there will be. That would be a question that would be raised about SMA. Do we need to be diagnosing these cases even before they're born to maximize the benefits of the therapies that are currently available?

The second question that's harder to answer is because the mechanism does not exist for gathering the information right now, and that's questions that were brought up by several other speakers regarding access to care. Who is lost to follow-up? Who is getting care? Who is getting care where? Who is getting adequate care? And what are even the most basic outcomes? Are they still alive? Are they receiving care? Is there growth and development and overall health? What's expected for the treated condition? Or are they doing better or worse than expected? Those very basic questions that are really public health questions, we don't have, as best I can tell, a good mechanism for collecting that information. That would probably require building some additional infrastructure. Thank you.

>> CYNTHIA POWELL: Thank you. All right. I'm not seeing any more hands raised. Anyone else have a comment? We have finished up a little early. I'll just ask Mia whether we want to go ahead with Alex's presentation?

>> MIA MORRISON: Thanks, Dr. Powell. I think, at this point, we do have enough time to move a bit ahead in the agenda and go directly to Dr. Kemper's presentation. So if you would just bear with us while we get his slides ready.

>> ALEX KEMPER: Okay. Fantastic. This is going to recap a presentation that we made earlier about what we've learned from the conditions that have been added to the RUSP. Reflecting back on this, what I'm going to tell you is a great story from the perspective of population health. And I think I'll also reaffirm the value and the importance of the work that the advisory committee has done.

I was really sort of moved when I was thinking about the positive outcomes that I'm going to be talking about when I just think about how difficult this past year has been with the pandemic and the really critical role that the public health departments and clinicians are playing in this difficult time. Obviously, I hope that everybody and their families are doing well during this period of time. But I think when you think about the context of the benefit of the

work of the advisory committees, it's really quite moving. Next slide, please.

So this is a report that we presented back in July of 2019. I'm going to be talking about what we have learned about newborn screening implementation for SCID, CCHD, Pompe disease, MPS1, and X-linked adrenoleukodystrophy. As you all know, SMA was discussed in a separate report. But in terms of providing a complete overview of things, we're going to be talking about SMA now. So we're going to be, again, primarily talking about what we have learned about the conditions that were added to RUSP between 2010 and 2018. If you want to go to the next slide.

So this is just a reminder of when the conditions were added to the RUSP starting with severe combined immunodeficiency back in February of 2010 through the most recent condition, spinal muscular atrophy, which was added back in July 2018. I will tell you that each condition brings forth its own unique special features and sort of lessons learned and those kinds of things. I've put some those on the slide. Again, we've discussed these in the past. I'm going to go through this presentation relatively quickly and stopping to point out what I think are important lessons. Next slide, please.

So again, this slide just summarizes the timeline between when a condition was first nominated. Some conditions were renominated, because when the advisory committee looked at the condition, there were gaps in the evidence that precluded recommendation to be added to the RUSP. You can see the various dates of when the vote was ultimately recommended and when the Secretary formally added something to the RUSP. Again, this is in the interest of just providing that historical background, and also I will show you the time period the evidence accrued. Next slide, please.

So this is the proportion of states that are screening for the conditions going through November of 2020. Again, things are changing rapidly, especially related to SMA. Next slide, please.

And this just takes the state newborn screening level data and reflects back to the proportion of births that are screened for each condition. Just to give the advisory committee a sense of the overall coverage. Again, this goes through November of 2020. You know, it's about a month out of date. Next slide, please.

So we discussed before the challenges to adding a new disorder to newborn screening. And I think it's important to keep this context in mind when thinking about the time period from when something's recommended to the RUSP or to when states might begin screening for it. So there's the personnel issues. There's the issue of getting the right equipment. There's the process of figuring out exactly how the screening approach is going to be done and the algorithms implemented. There needs to be a data information system for managing that and then there all the problems and challenges related to establishing diagnosis and follow-up. Next slide, please.

There are also facilitators in the same way that there are challenges in terms of peer resource networks. Piloted or implementation funding, HRSA, and the NIH and other federal agencies have been very helpful with that. There are issues related to the screening test itself and the degree to which it can be implemented with things that are already there. Advocacy groups are important in terms of understanding the evidence and adopting screening. Then there are all these other registry and systems that sort of follow into place as well. Certainly, if a state is mandated to implement something to the RUSP, it can speed up when it would actually begin. But I just like to always balance the challenges with the facilitators that we know that are out there. Next slide, please.

So I'm just going to go through at a high level some newborn screening outcomes. These slides, which are available to everyone, have a lot of information. We could spend, you know, days digging through all of this. Again, since we've presented some of this further, I'm just going to take a scenic drive through the slides. Here are some outcomes of some publications related to newborn screening for severe combined immunodeficiency. You can see the slides that are -- you can see the states that are listed and what their particular outcomes are. For me, it's really, I think, instructive and interesting to look at the positive screens that have resulted from newborn screening to give a sense of the population benefit that have accrued.

As I go through the slides, there are going to be, and this is going to affect more future slides than this one, but things like the positive predictive value. Again, the positive predictive value is, again, the proportion of newborns that screen positive that end up being confirmed to have the condition. And you have to take the positive predictive value with a little bit of grain of salt because there are so many variations in terms of how the findings are from the newborn screening are interpreted and classified. So I'd really, for the purpose of this conversation, just focus on the positive screens that have resulted from screening. These slides also give some information about the work that's required within the newborn screening programs in terms of the proportion that need to be retested and those kinds of things. Again, for the purposes of this, if I were going to pay attention to things, I would look at the number of cases that have been identified. Next slide, please.

So if you look at the published outcomes from SCID, there is one report that combines 11 programs and pilot projects that I pointed out on the previous slide. There's, as we know, for treatment, and this is just described in that study, most children are getting the stem cell transplant. In this one report of the 44 -- I'm sorry, whatever it is, 44 plus 4 plus 2, the 50 that were treated, there were -- here, I actually have it listed right there. There were seven children that died, but you can see the overall survival during this period of time of the infants that were detected through newborn screening is a remarkable 92%. As with any screening program, there are a lot of incidental findings. You can see those number of cases listed here. Next slide, please.

I'd like to turn next to CCHD. One of the most, I think, instructive publications that's been published about CCHD, was a publication in JMA from 2017. It was really a policy-level analysis looking at state screening policies and infant deaths related to CCHD. The key message from this report is that states that had mandated CCHD newborn screening policies had about a one-third reduction in deaths due to CCHD following the implementation of newborn screening. I think that this is one example of the population health benefit of newborn screening, again, looking at the policy level. Next slide, please.

So here's a bunch of individual studies that were done across different states. Again, you can get a sense of the large number of children that are being screened in each case as well as the proportion of children that are getting identified. A challenge with CCHD screening, when you look at the positive predictive value, is one of the things we have learned since newborn screening for CCHD has been implemented is that beyond critical congenital heart disease, there are other things that are detected that benefit from early intervention, things like sepsis. That's not necessarily captured in the positive predictive value when it's restricted just to CCHD. Next slide, please.

Here are the published studies that were included in our report related to newborn screening for Pompe disease. And you can see the total number of infants that were included in each report and the proportion who had a positive screen. You can see here, too, that the positive predictive values, you know, there's a large range. Again, some of this has to do with how things are counted and the methods used for screening. Next slide, please.

Again, this just further breaks things out. One of the big issues related to Pompe disease screening is the relative number of the infantile onset versus the late onset Pompe disease that's detected. There is a lot of concern about the number of individuals with pseudo-deficiency who would need to go through some diagnostic follow-up to ensure that it was truly pseudo-deficiency and not the -- not the true disease. And you can see how those numbers played out here. Again, it's not surprising that the numbers are small. Pompe disease is a rare condition. Next slide, please.

Here are the findings from MPS1. You can look across again and see the published studies, the number of cases that have been detected, reported in these studies through newborn screening. Again, here's another example of where the positive predictive value is highly variable. For example, the degree to which they're using post analytic tools, like the clear tool, which the advisory committee has talked about before. Next slide, please.

Here again are further studies. These are in alignment with the slide that I just showed before. Again, MPS1 is a rare condition, so the fact that any individual in one of these studies, there are not that many true positives is not surprising. Next slide, please.

Here is excellent adrenoleukodystrophy. You can see one study that was done in North Carolina and the other in Minnesota, along with a number of positive cases that were detected. With the ongoing challenges related to X-linked adrenoleukodystrophy is separating out affected males from women who can be affected or not affected. And you can see that in the North Carolina report, they didn't specifically break down differences in identification by sex, but they did in the Minnesota study. Next slide, please.

Again, here is further follow-up from the studies that I just presented again combined to make the positive cases a little bit easier to ferret out. Next slide, please.

Now let's move to SMA outcomes. If you remember, this was a separate report, but we've put it into this just to help with the conversation. So at the time of the report, New York had published their experience with screening for about 225,000 infants, and you can see the number of cases that were detected. One of the things that I think is particularly notable is the median day of follow-up at specialty centers after newborn screening for SMA was about eight days after birth, and it really speaks to the ability of the New York newborn screening program to really be comprehensive and effective with getting newborns to treatment. We did work with the Newborn Screening Translational Research Network, that's what the NBSTRN is, and the Association of Public Health Laboratories, APHL, and they are working with states in adopting newborn screening. Of the over one million newborns screened for SMA, at least 111 of them of unique infants have been identified with SMA. And so, again, it gives you a sense of the public health impact that newborn screening is having. Again, it's a rare condition, but from the evidence we've looked at before, there's real benefit from this level of early identification. Next slide.

So this is, you know, the easy one look at all the information I have just said. Again, I know it's a lot of information, but I think that if I were going to take one slide out of the whole thing, this would be the take-home message. You can see across the six conditions I spoke about rather quickly. You can see the total number of infants that were screened and the number of cases true positives that come from this. Given that these were conditions that benefited from early identification, I think that the advisory committee and others can really look at the real benefit and really understand the real benefit of newborn screening on these children and their families. It's, I think, really a remarkable accomplishment. Listed on the slide are the other positive screen results just to try to put things into context, and the bottom row lists how we put together the various publications. Again, this is like the real take-home slide from the presentation. So I'll just leave it up there for a second for people to look at. Next slide, please?

With that, I'd like to open things up for questions. As people have questions, maybe if we could just go back to the previous slide because I think that will help if any particular numbers come up.

>> CYNTHIA POWELL: Thank you, Dr. Kemper. Yes, we do have a few minutes now if there are any comments about Dr. Kemper's presentation. First, we'll take those from committee members followed by those from organizational representatives. And just as a reminder, please state your first and last names. If we don't have enough time during this session, we'll take this up again in the afternoon.

>> ALEX KEMPER: It looks like Dr. Baker.

>> MEI BAKER: Hi. This is Mei Baker, committee member. I just want a quick question, and I'm isolating on this SCID. So when you reported positive predictive value, that's cumulative; right? It's three reports and you're adding on together?

>> ALEX KEMPER: Exactly.

>> MEI BAKER: Okay. Because I know our program varies 50%. So I want to see 5.5.

>> ALEX KEMPER: Yeah. Again, I want to be very cautious by this notion of positive predictive value because states interpret what a positive screen is differently. Also, because algorithms are complicated and sort of the denominators change and that kind of thing. We had a lot conversations about even whether or not that line was valuable. I think looking at the true positives and the magnitude of the public health impact, I think, are the key lessons. There's just so much variability in what you might count as positive predictive value.

>> MEI BAKER: I agree with you 100%. For SCID, because we use leukopenia as a market because I feel like a state, if you do the assay, it's a SCID. So from program point of view, and your positive value would be lower for the analytical piece. I agree with you. I think each of these disorders have a unique situation.

>> ALEX KEMPER: That goes for every condition. For example, if you look at CCHD, really what states considers the targets in screening. It just continues. So we put that there just to kind of give context, but I appreciate it lacks nuance. And it doesn't appear in the final report as such. We just wanted to put that in for the purposes of conversation.

>> CYNTHIA POWELL: Anyone else?

>> ALEX KEMPER: And I appreciate everyone seeing these numbers before so they may not be new particular questions about it. I do think that, you know, it's kinds of inspiring to see what states have been able to do and the impact it's had on families.

>> CYNTHIA POWELL: Susan Tanksley. Susan, we can't hear you. You may be on mute.

>> SUSAN TANKSLEY: Hi. Can you hear me now?

>> CYNTHIA POWELL: Yes.

>> SUSAN TANKSLEY: Okay. Great. Susan Tanksley, Association of Public Health Laboratories. I wanted to comment first, I think it's fantastic that we have had as many publications as we have on these disorders. As I was reviewing information for this meeting, it really inspired me and made me think we really -- I'm about to get to hire an epidemiologist. I'm

really excited because we'll actually begin to be able to look at some of the data we have in the Texas program. But it brings me back to the conversation we were just having about data and having appropriate data to look back and see what difference are we really making. It's fantastic that we have identified this many cases, but it would be really, really great to be able to look at the long-term data that's been collected. Hopefully, it's being collected on these children so that we can see the true impact and how we really can improve their outcomes.

>> ALEX KEMPER: If I can just add on to what you just said, Dr. Tanksley. The data that we have shared with you is primarily from publications that work from the Newborn Screening Translational Research Network and APHL. So I know that other states likely have information that would contribute to this sort of thing. And so to the degree to which we could get access to that and, of course, you know, with all the other things that states have going on. But to publish their findings in the peer review literature would be great.

>> CYNTHIA POWELL: Georgianne Arnold?

>> GEORGIANNE ARNOLD: Georgianne Arnold from Society of Inherited Metabolic Disorders. You actually just answered my question, which was what would this look like if you added all of the state website information, particularly for CCHD, which, sadly, only had 10 positives reported. Really, we have many more.

>> ALEX KEMPER: Yeah. To the degree that that could be put together and also, I think, gotten out into the peer reviewed literature I think would help, you know, shine the light on the real benefit that it's had. Unfortunately, for the purposes of this work group, we weren't able to do that. Again, I just refer people back to specifically CCHD for that study that looked at changes in CCHD-related or I should say infant mortality associated with adoption of newborn screening for CCHD as being a really compelling argument about its impact.

>> CYNTHIA POWELL: Robert Ostrander.

>> ROBERT OSTRANDER: Hi. Robert Ostrander, American Academy of Family Physicians. The long-term follow-up and treatment subcommittee was kind of on a roll dealing with the number of the issues brought up both in the previous discussion and today about continuing to look forward with these conditions that we approve and then assessing the effectiveness and our impact. Unfortunately, between the reauthorization issue that we had and now the COVID-19 thing, we have kind of lost our momentum. But we presented to the committee, it looks to me, and I didn't bring it up before. I had to dig back through my documents. But it looks to me like the end of 2017 we sent a long report to the committee on what was called quality measures in newborn screening and long-term follow-up that provided something of a potential framework that we might ask to be implemented or used as we go forward and look at true long-term follow-up, both metrics and how people are plugged in.

One of the things that with the long term follow-up treatment subcommittee, we actually suggested to the committee, this goes to our previous discussion of what we expect when conditions be added to the RUSP, is that there be some sort of denominators that provide some sort of blueprint for what long-term follow-up and treatment might look like so that we can be -- I mean so that require a plan at least to do that be included with the implementation if something gets added to the RUSP, so that we know there are -- there's going to be a network of folks that are attracting outcomes. And our paper discussed the kind of things that we thought were important to be tracked so that we don't have to be mining data from this place and that place in published report. Also, again, when we talked about Pompe in terms of unexpected course of illness. With all these conditions here, as we get four, five, 10, 15 years out, that we have some real outcome metrics to tell us. So my suggestion is, number one, that the committee look at the work product or the long-term follow-up treatment subcommittee

that's already in place; number two, that one of the things that we should ask of nominators is to perhaps somehow include in the requirements for adding something to the RUSP, that there be some blueprint. Again, I think it would be foolish to ask for things to be laid out, but some blueprint or vision of how long-term follow-up treatment measurements would be done.

>> CYNTHIA POWELL: This is Cynthia Powell, committee Chair. Thanks for bringing that up. We were actually planning initially to have a roundtable discussion about just those issues at this meeting, but then for various reasons had to postpone it, but we are definitely planning to do that at our next meeting. So looking forward to that. Debra Freedenberg?

>> DEBRA FREEDENBERG: Hi. American Academy of Pediatrics. Rob just said a lot of what I wanted to stay, as did Susan. But the first thing is that there's a lot more data out there than the published data. States have tons of data. Some are willing to share. Some aren't. Some are just too busy with what they're trying to do day to day to put all of the things together. As you have alluded to, we happen to be a huge program, also the newborn screening program part of newborn screening program in Texas. We just don't have anybody to put the data together to share it, which hopefully will change.

But what I've seen is that the information and funding and follow-up all tends to get siloed. There is a lot of the newborn screening program is responsible for this. The rest of the system is responsible for that. You know, it doesn't really follow the child. The workforce issue, well, that's the clinical problem. It's not the newborn screening program's problem. And I think we really -- it would behoove us to take a more kind of holistic approach and look at it as an overall system, because newborn screening programs really are not in isolation. We're in partnership with the clinicians, we're in partnership with the metabolic docs, and all the other specialists that are out there. So I think that we need to look more holistically and stop kind of spiraling things quite as much as we've been doing.

And then the last thing that I wanted to mention is that long-term follow-up has been very much on a lot of folks' minds for a variety of reasons. At a state level, we've embarked on the long-term follow-up and many of the public health measures that were described before, the ones that we are now starting to follow, and we are just at the beginning, so we can't tell you what our numbers are. We know we get better follow-up with that, but just looking are you alive, are you in follow-up, do you need anything, you know, what are your barriers to care, do you need help, those kinds of things. So we're beginning to do that. And I don't think we're beginning to look at thinking about what is the newborn screening program's responsibility on the public health side, and then what is the long-term follow-up responsibility across the clinical spectrum?

>> CYNTHIA POWELL: Annamarie Saarinen.

>> ANNAMARIE SAARINEN: Hi. Annamarie, committee member. Alex, thank you for this really good overview of these conditions that were added over the past decade. I'm actually grateful to say that I've sort of been here for all of these, not on the committee, of course, but I was at the meeting where SCID was formally advanced by the committee and then, I think, that was probably the first presentation by Dr. Rinaldo for CCHD at that same meeting, as I recall. It's been really fascinating to learn from each of these along the way.

I wonder what's your recommendation, I guess, from a committee perspective or how we -- do you somehow -- by we, I don't mean the committee necessarily, but the community -- do a better job of being able to see something more than a snapshot or a summary of these screening results? And I realize it's basically like doing a meta-analysis times 20. What are your thoughts on that so we can get a better picture?

And then just to address the CCHD numbers. I don't necessarily view the ten true positives out of -- that that cohort that's represented there is necessarily a sad finding, but it's sort of a little bit of a reality of when those papers were published, sans maybe the last two, because we were still thinking very narrowly about the definition of critical congenital heart disease, and there was a lot of reporting variables and variances between the states. So some were -- you know, would count a pick-up of a congenital heart defect that wasn't on that core list of seven or eight conditions and they wouldn't report it as a true positive case because it wasn't on the list, per se. Where, of course, now we know. We pick up something because that list has expanded beyond those original eight targets that we thought we were going to find. You know, this sort of review of the older data doesn't kind of reflect that nor how we're capturing in the case of pulse oximetry, but the secondary but important conditions. All of that is sort of evolving. I think these numbers are certainly changing all the time. How best do we, as a community and maybe as a committee, better demonstrate, I think, the good or the bad or the real numbers around this? I mean, is it a NewSTEPs collaboration, or NPHL and NewSTEPs? What is the thought process on being able to really see the impact and reassess over time?

>> CYNTHIA POWELL: Alex, did you want to comment?

>> ALEX KEMPER: Well, there's actually a whole series of points that you just made, all of which I agree with. So these studies represent some snapshot and they're variable in how they count. One of the takeaways from CCHD actually doesn't even show up in this table, which is that difference in policy studies that was published in JMA which I actually think is a really compelling way to look at benefit in the absence of having the granular individual level patient stuff that, ideally, we would have. Maybe there are lessons from that as well. But the other issue in terms of how is the information going to be collected? And so I do know that the NewSTEPs is engaged in this with APHL. You know, I want to give them credit for that. I should actually give Dr. Lam a lot of credit as well for helping me find out this stuff and put it together. I didn't mention that at the beginning, and I feel remiss for not doing so. But regardless, there's different ways that these things are counted and it takes a lot of work to do it. I think that the comments that Bob Ostrander made before about having standard metrics for reporting would be great. Debbie Freedenberg brought up issue that state newborn screening programs are collecting this information, but they have, like, a million things going on as well. Ultimately, like, whose responsibility is it to be collecting or reporting this data? And what can we as a community do to encourage that those data are reported on some sort of regular basis, I think, is an open question. So I'm not going to give you a specific answer to that and maybe duck it and turn things back over to Dr. Powell to see if she has comments or wants to engage the advisory committee on that.

>> CYNTHIA POWELL: Yeah. This is Cynthia Powell, committee Chair. I certainly think it's a very important issue and one that the committee is trying to address and will continue trying to address this. I would say specifically for CCHD, a problem amongst states is that there's, you know, very limited reporting, you know, even compared to metabolic disorders. You know, where that information is placed regarding the pulse oximetry measurements and things, you know, it's not well tracked. That's certainly, you know, something that I think is very important to do. So hopefully, as time goes by, there will be better ways to have this interoperability system so that one hospital could communicate information with their state. Definitely an important thing to address.

I think we'll take one more comment. Jacob Hogue?

>> JACOB HOGUE: Jacob Hogue, organizational representative for the DoD. In following on the discussions about long-term follow-up as well as the previous discussion related to the decision matrix, one thing that came to mind was as we look even five or ten years out and looking at the data that's available, the available data tends to be more about the more severe

disorders and the conditions. Thinking about how that reflects looking at the data here, as we were talking about CCHD and other conditions that may be detected by positives or looking at the late onset Pompe disease. For example, for looking at outcomes, we have a possibility of having some confirmation bias there where we're looking at all the kids who have infantile onset Pompe disease and seeing the positive outcomes that occurred from screening. And for applying that back to the decision matrix and thinking about the net benefit for all people who are screened, and that the data available at five or ten years may not take into account the impacts that has on those that are identified as being carriers or late onset or false positive screens. I think very important to look at long-term outcomes but acknowledging that the long-term outcomes that we have may actually be biased towards getting us some confirmation bias for the more severe disorders.

>> CYNTHIA POWELL: Thank you. All right. Thank you, all. Thank you, Dr. Kemper and all of you who commented.

As with all of our committee meetings today, there is an opportunity for members of the public who have previously registered to provide oral or written comments. The committee did not receive any written public comments. The committee will now hear oral public comments from three individuals. First, we will here from Dylan Simon from the Every Life Foundation.

>> DYLAN SIMON: Dr. Powell, can you hear me now?

>> CYNTHIA POWELL: Yes, we can. Thank you.

>> DYLAN SIMON: Sorry about that. Thank you. On behalf of Every Life Foundation for Rare Diseases, I would like to thank the committee for providing me the opportunity to address you today. Again, my name is Dylan Simon, and I'm the newborn screening and diagnostic policy fellow for Every Life Foundation for Rare Diseases.

I want to thank multiple members of the advisory committee and the evidence review group who spoke at last month's annual newborn screening boot camp. We were thrilled to have your expertise and perspectives engaged with a wide variety of newborn screening advocates to help empower patient communities working within the newborn screening ecosystem. The boot camp, which is in partnership with Genetic Alliance, was a five-week event designed to educate and engage newborn screening stakeholders. We were delighted with the success of our virtual event with more than 280 individuals attending at least one week of the boot camp. Over the course of the first four weeks of boot camp, discussions included a wide variety of newborn screening related issues from the importance of building coalition to the challenge of state implementation. We were able to discuss important topics such as the benefits of patient registries, better interview process of the federal advisory committee, and how patient advocacy organizations and public health laboratories can work together to move the newborn screening system forward.

We closed the boot camp with three distinct discussion groups designed to broaden opportunity for communities to dive deeper into the information covered during the boot camp. Advocates were asked to self-identify into one of three groups, just getting started in newborn screening, on the path to RUSP, and beyond the RUSP. With community moderators helping to answer questions, participants shared ideas and best practices on how to address the common challenges that most face in the community. Thank you again to the entire newborn screening community for your support of the boot camp. We appreciate that the COVID-19 pandemic has placed even greater demands on the commodities of time resources of our newborn screening leaders, and we are especially grateful for the dedication to patient communities. It's through conditioned support that we can bring together a diverse group of stakeholders that their unique perspectives on how to move newborn screening forward.

We are excited to announce the third annual newborn screening boot camp will occur next October, hopefully in-person, before the Newborn Screening Symposium in Sacramento, California. We are looking forward to seeing everyone in-person at next year's event. We are excited for all the great work that's occurring within newborn screening's base and look forward to continuing to advocate effectively to navigate engagement in the community. Thank you again for the time.

>> CYNTHIA POWELL: Thank you very much. Now, we will here from Stephen Holland.

>> STEPHEN HOLLAND: Hello. Can you her me?

>> CYNTHIA POWELL: Yes.

>> STEPHEN HOLLAND: Thank you very much for the opportunity to speak. I'm Stephen Holland, the proud father of three children with mucopolysaccharidosis type 1, and Vice Chair of the National MPS Society.

The society was founded 46 years ago with the mission to cure, support, and advocate for the mucopolysaccharidosis and mucolipidosis diseases. We serve individuals, families, and friends affected by MPS and ML by supporting research, families, and increasing public and professional awareness. All 15 known subtypes of MPS/ML diseases are rare genetic lysosomal storage diseases caused by the body's inability to produce specific enzymes. The missing or insufficient enzyme prevents cells from recycling waste, resulting in storage of materials and cells through the body. As the disease progresses, there is systemic damage throughout the body, including the heart, bones, joints, respiratory system, and central nervous system, leading to widespread physical and developmental challenges and a shortened lifespan. Due to the progressive nature and irreversibility of the damages, especially to the brain, it is imperative to diagnose these diseases as early as possible to enable more effective intervention. To date, about half of the MPS and ML subtypes have FDA-approved treatments, with over 20 companies working on new treatments at various clinical stages. With well-defined biomarkers and available low-cost tests, the MPS and ML diseases are prime candidates for consideration to newborn screening.

A few years ago, I spoke to the committee and we worked closely with you to nominate MPS1 for nationwide newborn screening. Since its inclusion in the RUSP, MPS has been included in the newborn screening programs of 21 dates and the District of Columbia, enabling newly diagnosed patients to access treatments and interventions as newborns. With the collaborative efforts from our academic and industrial partners, the society has recently submitted the nomination package for MPS II. In parallel fashion, the nomination work for MPS7 is also underway. Our goal is to work with the committee over the next few years to submit nominations for the remaining MPS and ML diseases with effective therapies.

On behalf of the MPS and ML communities, we thank the committee for its leadership role and landmark work to build the nationwide newborn screening system in the U.S, especially with a clearly defined pathway for new conditions to be nominated. We look forward to continuing to work with you to address the critical need of newborn screening for the MPS and ML communities in the days and months ahead. Thank you.

>> CYNTHIA POWELL: Thank you very much for your comments. Our last public comment for the day will be from Ryan Colburn.

>> RYAN COLBURN: Hi. Thank you for having me here today. Following the previous discussion, I think this sets me up very well. I would also like to clarify that I did submit a written

comment, which is an expanded version of this. Hopefully, that made it through.

Starting out, dear members of the Advisory Committee on Heritable Disorders in Newborns and Children, my name is Ryan Colburn and I have Pompe disease. I was diagnosed five years ago. After an initial adjustment period, I have leaned into the rare disease ecosystem and found that there is an incredible amount of great stuff happening to positively impact my future and, more importantly, improving our collective future as manifested through newborns and children.

On the personal side, I have spent my career in engineering and operations management roles, working in Formula One racing, airplane builds, and currently on reusable rockets and satellites. It's fair to say that I'm a nerd and it would be reasonable to assume that I love data. This statement and my written submission are in support of the importance and power of data and to advocate that making as much deidentified data available to as wide an audience as fast as possible is a winning strategy to support improved health for our newborns and children.

I would like to propose to this committee an emphasis on realizing data as an opportunity to use newborn screening as a vehicle to accelerate the rate of development of new knowledge in rare diseases through supporting a model which makes deidentified data easily available to the public with minimal latency to report. When we share this data, we amplify the opportunity for the next bright pre-med student to study rare disease, helping newborns and children, and the next researcher, the next pharmaceutical company, the next patient advocate, brother, sister, mother, father, and neighbor. We would give them all the chance to contribute, and you would give me a chance to contribute. I want to help advance progress for Pompe and other rare diseases. And we have a motivation and interest and a background with what this data means along with an overall perspective that is unique compared with the current siloed data model. With our motivation and varied backgrounds, we have a desire and ability to contribute.

Currently, the effort required to compile the data for any of these roles prohibits us from contributing to the development of new knowledge in rare disease. There is, however, data with a huge potential to be useful that is collected through federally supported programs, but that data is not publicly accessible. As we heard from some of the speakers, it's not even accessible to some of you. For an additional information and an example of doing things the hard way, please see my written statement that I've submitted which includes an analysis of data I have compiled over the last year through scouring papers and reaching out to states and countries directly to understand Pompe incidents through their newborn screening experience. Incidence is a fundamentally important figure in understanding the disease, and this data shows a clear convergence that excludes the currently most cited projections. This data tells a compelling story that we are collecting data now that has the potential to teach us more about our disease than we have ever known. Collecting data and, more importantly, using that data is the key to unlocking this learning. I think this example is easily transferrable across all rare disease.

In summary, newborn screening really is the coolest game in town, but we've only scratched the surface of what is possible when we empower and activate our rare disease community with timely access to data. We stand at the door of an opportunity for an inflection point and progress for our newborns and children and their families impacted by rare disease. We can realize this opportunity by taking an open access policy to data, even while honoring our duty to protect the privacy of individuals' data. I'd love to engage in a discussion. I know that this isn't the format for it. But in my written comments, you can find my contact information. I'd be happy to talk about Pompe and perspective on other rare disease and how data that we're getting out of newborn screening can really change the landscape. Thank you.

>> CYNTHIA POWELL: Thank you very much. And I want to let you know that your written

comments were distributed to the committee members.

All right. Next, we're going to take about a 40-minute break, so I can stop coughing, and we'll reconvene at 1:00, 1:00 PM Eastern time. Thank you.

Break.

>> CYNTHIA POWELL: North Carolina at Chapel Hill. He completed his residency in clinical genetics and postdoctoral research at Baylor College of Medicine before joining the faculty at UNC in 2009. He has a clinical appointment in the Department of Medicine, Division of Hematology, Oncology, and the Lineberger Comprehensive Cancer Center, and is Director of the UNC Cancer and Adult Genetics Clinic. Dr. Berg's research group examines the application of genomic sequencing approaches in clinical care through translational research projects studying diagnostic indications as well as screening in healthy populations. In addition, Dr. Berg is a PI in the Clinical Genome Research, also known as ClinGen, Consortium. He was co-PI of the NC NEXUS Study. He continues to work on implementation of genomic screening in a clinical setting across a variety of age groups.

After Dr. Berg's presentation, we will hear from Dr. Robert Currier. Dr. Currier retired in 2018 from the California Department of Public Health where he spent over 20 years as the chief statistician of the Genetic Disease Screening Program. His primary responsibilities were the ongoing monitoring of the newborn and prenatal screening programs, the evaluation of the impact of proposed program changes, and the analysis of confounding factors that interfered with accurate screening results. Themes in his current research include the evaluation of complex multianalyte profiles for disease evaluation, finding ways to get early indications of the progress of therapy in infants, receiving gene therapy, or HSCT, for severe combined immunodeficiency and other disorders, and the ethical, legal, and social implications of evolving genetic technology.

Following Dr. Currier, we will hear from Dr. Stephen Kingsmore who is president and CEO of Rady Children's Institute for Genomic Medicine where he leads a multidisciplinary team of researchers and clinicians. They specialize in the fastest use of whole genome sequencing to identify rare genetic disorders and help critically ill newborns and children in intensive care to receive rapid precision medicine. Among his achievements, Dr. Kingsmore holds the world record for the fastest molecular diagnosis using whole genome sequencing in just 19.5 hours. Dr. Kingsmore received the Bachelor of Medicine in surgery, obstetrics, science, and Doctor of Science degrees from the Queens University of Belfast. He trained in clinical immunology in Northern Ireland and did a residency in internal medicine and a fellowship in rheumatology at Duke University Medical Center.

Finally, we will be hearing from Dr. Robert Green who is a physician, scientist, and professor of medicine at Harvard Medical School who directs the Genomes2People research program. His empirical research and policy development is accelerating the implementation of genomic and precision medicine. His work has established the safety and feasibility of disclosing various forms of genetic risk information, assess the impact of whole genome sequencing in primary care, created the concept of aggregate penetrants of genomic variants in a prospective population cohort, and provided early data on the clinical utility and cost-effectiveness of genomic sequencing in healthy adults, the MedSeq project, in newborns, the BabySeq project, and in active-duty military personnel, the MilSeq project. Dr. Green has established the world's first academically affiliated, family-oriented preventative genomics clinic in Boston, cofounded a tech-enabled tele-genomics company, Genome Medical.

With that, I'd like to turn it over to Dr. Berg.

>> JONATHAN BERG: Great. Thank you so much for the invitation to speak today. As Cindy said, I was the co-PI to Cindy during the NC NEXUS project and it certainly was a really great experience. Can I go to the next slide?

So I think part of the inspiration for the NSIGHT consortium comes from many of the sort of predictions that started coming out around the uses of genomic sequencing as it really became clear that soon, and currently, that is now, the cost of sequencing genomes makes it accessible for many different purposes. This is a quote from Frances Collins that suggests that as we learn about effective interventions for genetic risk factors and recognize that interventions early in life provide significant advantages, it will become more and more compelling to determine this information at birth. That's really the nature of what newborn screening is really about. Next slide.

So for the NC NEXUS project, which is the North Carolina Newborn Exome Sequencing for Universal Screening. I'm sorry if there are some animations here. We sequenced two cohorts of patients. One of them came from a healthy pregnancy, so these were healthy newborns, and we recruited the parents and enrolled them in the study prenatally, so while the pregnancy was still ongoing, so that they would have some time to review, study materials, and so forth prior to the birth of the child. The second cohort was a group of infants and children who came from clinics at UNC who already had conditions that had been identified through newborn screening, so we were able to take patients from the metabolic clinic, for example, and from the hearing loss clinic, and essentially used those patients as a way to gauge how well the sequencing would have identified diagnoses. We defined several different categories for result disclosure that's defined by clinical actionability. I'm not going to go into the details of how we defined clinical actionability, but that wok has been published. I'll show you the categories in an upcoming slide. All of the parents completed an online decision aid, so quite a lot of the research had to do with how parents would engage with material that was trying to educate them about the exome sequencing and what kind of information they could learn. I'm not going to present anything about that today. That's work that was led by Don Bailey at RTI. Everyone in the study essentially received results for what we defined as the next generation sequencing newborn screen, which would be our childhood onset actionable conditions. This would include anything that was on the current recommended uniform screening panel as well as other conditions that we felt met similar criteria. And, of course, not all patients will have received anything from those categories. The parents were then randomized to two groups for a study of whether they would be interested in additional genomic findings outside of the conditions that would be typical to newborn screening. They were either randomized to a decision arm or a control arm. There's extensive parental survey research that was done in this study. I won't have time to present much of that. That was largely led by Chris Rini, and there will be kind of interesting findings about what the parental preferences indicated. Next slide.

I just want to start by mentioning the team. Obviously, projects like this have very large number of participators. Cindy and Don and I kind of served as the leadership of the grant, but there were a number of people in the lab and in the clinic that helped with this project.

So, as I mentioned, there were several categories of information. We defined this based on whether it met a threshold for clinical actionability. Conditions that we felt were childhood onset and medically actionable were put into the NGS/NBS category. As I mentioned, we reported to all participants if they had any. Then we had a category of excluded information, which would have been adult onset, nonactionable conditions, and we decided as a group simply not to report them to any participants for obvious reasons related to ethics of genetic testing in children. But then there's a middle category of additional information that maybe are conditions not quite meeting the threshold of actionability or statuses like carrier status for recessive disorders, or adult onset medically actionable conditions which were part of this sort of additional randomized trial where we wanted to address parental preferences and kind of

potential psychosocial implications of having to make decisions about that information. That was in the optional category for those that were randomized into the decision arm. Next slide.

And I just want to preface that I'm going to show some of the molecular results. It's really important and you all are quite familiar with the idea of sensitivity and specificity and how that affects the false negatives and false positives of any given screen. You know, clearly, with analyte tests where there is a nice difference in the distribution of the blue and the red analyte concentrations between unaffected and affected individuals, when we look at a genetic variant, we are essentially assigning it to a qualitative classification from benign or likely benign to likely pathogenic or pathogenic, and then a large category of variants of uncertain significance in between. Although here's not really any way to quantify the probability of pathogenicity, the guidelines for sequence interpretation tell us that variants that are essentially 100% known to be pathogenic are called pathogenic, variants that are greater than 90% likely to be pathogenic are classified as likely pathogenic, and then you have your known benign and known and likely benign categories. The variant of uncertain significance category is certainly very, very wide. I would argue that for genetic testing, where we gain sensitivity comes from how far into the VUS' we want to report things, because those are variants that might be pathogenic, but they also might not be. That also then affects the specificity of the test because, again, those variants may not be pathogenic. Next slide.

Using genomic sequencing as a screen really leads you to this problem of positive predictive value. If we were to restrict the variants of returning only the known pathogenic variants, which would essentially have 100% specificity, we would sacrifice the detection of some true positives because those variants might be rare or private and would not meet our threshold for a known pathogenic variant. If we dropped our threshold for specificity and included results with anything less than 99.99% specificity, we would have more false positives than true positives in a large population screen and that would then have downstream costs and consequences that would be, you know, important for us to consider. Next click.

So in metabolic conditions that are already on the newborn screen, we can set a threshold so that we get a certain number of false positives, ensuring that we pick up all of the true positives, but then use a secondary test to essentially confirm or refute that initial screening finding. And the challenge for a molecular test is that we don't always have a secondary enzyme test or other analyte that we could use to verify that finding as being pathogenic. So it really raises the question of whether we should even be thinking about using the likely pathogenic results, which, as I mentioned, could have as much as a 90% likelihood of pathogenicity, which in a population screening would give you massive numbers of false positives, versus should we taper the degree of variant return based on what types of available follow-up there are. So we'll come back to that at the end. Next click.

So in NEXUS, we basically took these two different cohorts and we assigned the analysts to the cases without telling them what cohort they came from. Essentially, that first molecular analysis was done blinded to whether this was an affected or unaffected individual. The analysts looked at all of the genes, all the variants of the genes that were in the next gen sequencing newborn screen and would report essentially the variants that we thought were pathogenic or likely pathogenic in this case, and the result then would be a positive or negative screen result. After that happened and the analyst had registered their results from a blinded analysis, they were then unblinded so that they could know whether it was an individual from the metabolic cohort, for example, or the hearing loss cohort, and then they were going to look at a second list of genes that would be included for diagnostic analysis of those -- the relevant genes, essentially. In this case, we would return a positive, negative, or inconclusive result, which would include the VUS'. This way, we would be able to return results to patients with one of the -- from the affected cohorts to give their molecular results, but also to evaluate how well the screening would have done if we had only resulted as a positive or negative screen. All of

the results were confirmed in the lab at UNC and reported through the official electronic health record. Next slide.

From the affected cohorts, we had 17 metabolic patients and we were able to identify clearly causative variance for 15 out of the 17 without even knowing that they had that diagnosis, so a fairly reasonable clinical sensitivity, although small numbers. We had a couple of false negatives which were very interesting. One of them was due to a single heterozygous pathogenic variance in the gene associated with maple syrup urine disease in a patient with maple syrup urine disease, so this is probably an example where the second variant is not detectable by the exome sequencing either because it's a deletion that we weren't able to identify or a deep intronic variant that affected splicing in some way. Those types of false negatives are going to depend on the sequencing technology that's being used and what the analytics are to look to the variants. The second false negative we think was a homozygous missense variant that's a variant of uncertain significance in the MLYCD gene in a patient with carboxylase deficiency. So it's very likely that this missense variant is the cause of that patient's disease, but it was a unique variant. It hadn't been reported previously, so it was a variant of uncertain significance.

Both of these are reported as inconclusive on our diagnostic report. And I think it's appropriate if you're thinking about a patient with MSUD to report a single heterozygous pathogenic variant. And if a patient had decarboxylase deficiency, you would want to see that the homozygous missense variant. And so from a diagnostic standpoint, those make sense. The question would be how often would you find a carrier for MSUD in the healthy population? In fact, you would find that at a much higher rate than you would actual patients with MSUD. So reporting all carriers for MSUD would lead to a large number of results. Similarly, you would be reporting a lot of missense variants of uncertain significance if you allowed the results to be returned as a VUS. In the hearing loss cohort, we didn't have quite as high a clinical sensitivity. In fact, only about five out of the 28 patients had a clearly diagnostic result. There's a number of reasons for this. In part, because hearing loss might be nongenetic. There were some additional results that we felt, after unblinding, would be reasonable to return as an inconclusive finding, and so this may be a less efficient way to screen for hearing loss than actually using the phenotypic screening. Next slide.

Essentially, the full cohost of patients and looking at the genes, we included the NGS NBS. This would be outside of the categories that would be seen in the hearing loss group. We found a patient with a heterozygous LDLR pathogenic variant for familial hypercholesterolemia. That was not known to us when the patient was enrolled, but the family did report a family history of hypercholesterolemia, so it made sense in retrospect. We found a novel splice variant in a DSC2 gene associated with a type of cardiomyopathy. We found a patient with heterozygous factor 11 variants that probably indicates a bleeding disorder, and a female which was heterozygous for and OTC pathogenic variant. We reported this. She also had PKU, which was interesting. But she had this additional OTC pathogenic variant that was probably a hypomorphic variant and was actually found in some of her male family members. Next.

Of the additional information that could be obtained by parents randomized to that additional part of the study, I'm going to go to the next slide. Go ahead and click. Sorry, I shouldn't have put all these animations in. So there were 45 parents out of the group that were randomized to the decision arm, and 41 of them requested at least one other category of information. This could indicate how motivated the parents were to participate in the study. It's unclear whether 90% of the general population would have requested at least one other category of information, but that certainly indicates that there is great interest among parents for this type of information. And 34 of them asked for all three categories. We did find one adult onset medically actionable finding in one of these children, so it was a gene associated with increased risk for ovarian cancer. We found a child with actually what looked like a

nonmedically actionable diagnostic finding. This child actually, unknown to us when enrolling, at least to the molecular side, was enrolled because of hearing loss, but also had a very complex medical history, including some renal problems. Putting everything together, it looks like this nonmedically actionable finding is actually the diagnostic result for the child's complex medical condition.

So thinking about genomic sequencing as a screen, you'll hear from others that perinatal period is certainly a difficult time to conduct informed consent. That may be different when there is a child with a phenotype that needs sequencing immediately for making a diagnosis than it would be for a parent of a healthy child. We should be thinking about our tolerance for false positives and overdiagnosis. Here I'm defining overdiagnosis as the increased or the molecular diagnoses that are made in people where, due to incomplete penetrants or variable expressivity, they may never manifest in terms of those conditions. They will always have a molecular diagnosis but not necessarily develop clinical systems. That would be a type of overdiagnosis. Between those two things, we need to be thinking about how to gauge what we return, what types of variants, and what conditions we return, thinking about the consequences of missing a diagnosis, thinking about the availability of gold standard follow-up tests, what would we be recommending for the management plan subsequent to that molecular diagnosis, and what would be the economic impact and the societal consequences of doing that. It's going to require a great deal of additional work to be thinking through what would make sense for a next generation sequencing newborn screening. I would argue that we should be starting with a subset of the most well understood, highly actionable conditions that could be analyzed in a targeted way in newborns rather than exome or genome sequencing. That's, I think, a -- my personal conclusion from the NC NEXUS study. Next slide.

The things that we've been working on in my research group now are really thinking about age-based genomic screening, so thinking about how we could integrate population level targeted genetic screening for highly actionable age relevant conditions and working those into routine wellness visits for newborns and children. If you can just click again. We would envision that there may be several time points during pediatric care in which you could offer genomic screening for conditions relevant to those age groups. This might avoid some of the challenging ELSI conditions related to sequencing in newborns and children, allow parents to focus on things relevant to their child at that time, and not necessarily front-load everything on newborn screening. Finally, the advantage of this would be that it gradually introduces genomic screening to children over time. As they become adolescents and they start to engage in this decision-making process, they'll actually be even more prepared to engage in making decisions about adult-onset conditions or their own health screening in adulthood. So this is the paradigm that we're currently working on. And I use that the quote from Frances Collins. You can go ahead to that. I slightly modified Dr. Collins' quote to say that it will become more and more compelling to determine some of this information at birth and other information throughout the individual's lifespan.

I think that's the end of my slides. I think I have an acknowledgment at the very end. Thank you.

>> CYNTHIA POWELL: Thank you, Dr. Berg. We will have time at the end of all of the four presentations to take questions and comments from the committee members and organizational representatives.

Our next speaker, as I said, will be Dr. Robert Currier. We'll just bring up his slides. All right. Go ahead. Bob, we can't hear you.

>> ROBERT CURRIER: Sorry, I was on mute.

We would like to thank the committee for the invitation to present some of our results. Next, please.

I have no financial interest to disclose. Next, please.

The fundamental questions that the NBSeq study sought to answer were whether whole exome sequencing could replace MS/MS screening for inborn errors of metabolism and how WS could supplement or augment MS/MS screening. Next, please.

Our answer to these questions and our evidence was recently published in Nature Medicine. I only have time to present an overview of our approach and the results. Next, please.

To address our main question, we sequenced dried blood spots obtained from the California Biobank Program under an approved protocol to sequence deidentified samples. The biobank includes dried blood spots from all the newborns screened between 2006 and 2013. There were 4.5 million children born and screened in this period. From these, there were a total of about 1,300 affected with any screened metabolic disorder. We requested the comprehensive set of these. We also requested all 13 known cases where mass spec failed to identify a screened metabolic disease. In addition, we were looking at about 400 cases where mass spec screen was positive, but these newborns were ultimately found to be unaffected. Next, please.

The false positive samples were not a random sample. They consisted of all the false positive results for six screening tests, PKU, MSUD, IVA, VLCAD, LCHAD, and GA-2. These were selected because they have large numbers of false positives or because the overlapping profiles in the MS/MS screen make the differential diagnosis more challenging. Samples from the NICU were excluded to avoid the effects of prematurity in treatment. Next, please.

Of the 1,728 requested samples, 538 were omitted from the study because of budgetary restraints, diagnosis with a non-screened disorder, or failure of quality control on the resulting DNA. The remaining 1,190 exomes were divided into a validation set of 178 and a test set of 1,012. In order to model newborn screening, it was essential that the interpretation pipeline be completely automated. The analysis of the validation set showed that it was necessary to include rare protein altering variants of an MAF of less than 0.005. Next, please.

Of the 674 affected cases in the test set, only 377 would have been identified using curated variants. Including rare and predicted variants brings the total to 571, but that still leaves 103 missed by exome screening. Next, please.

Waiting for disease prevalence, exome screen had had a sensitivity of 88% and a specificity of 95%, which compares unfavorably with current MS/MS screening. Restricting to only curated variants improves the specificity with a significant hit to the sensitivity. Next, please.

The sensitivity varied by disorder. For many, the exome was 100% sensitive. And for BKT, the exome found both cases where analyte screening missed one of them. Next, please.

However, even in some canonical newborn disorders like PKU and MCAD, the exome pipeline failed to identify some individuals. The secondary conditions and additional conditions group showed similar overall sensitivity. Next, please.

Because the study included the false positive results for PKU, we had the opportunity to examine the performance of sequencing as a screening test for PKU. The first point to notice is

that of the 108 variants identified in the study samples, 23 or roughly 20% were absent from Clinvar. Next, please.

Using the recently published guidelines for variant classification in from ClinGen, only six could be called pathogenic with the remainder being variants of uncertain significance. Next, please.

Using the results of the clinical follow-up of positive PKU screens, we can divide the study cohort into five groups, 67 classical PKU, 27 variant H-PHE, 34 benign H-PHE, 31 false positive screens, and 1,023 negatives. PKU is an autosomal recessive condition wherein mutations in both copies of the gene lead to disease, so we can now break down each of these phenotype groups further by the number of variants they had in the PAH gene. In green are individuals who had two variants flagged in PAH by the pipeline. Of the 128 cases diagnosed clinically with either classic PKU or H-PHE, the predominant majority, around 94%, had two variants. Among the 1,023 PKU controls, there were 30 with a single PAH variant, which is roughly 3%. This frequency is consistent with the expected carrier frequencies in the ethnic group represented by the screened population. Most interestingly, among the 31 MS/MS false positive cases, we found that 16 of them, around half, also had two variants in the PAH gene. Next, please.

Delving into the cases that had two variants, we can now break these by the pathogenicity classification of each variant within the pair. Next, please. Now, back, please. I guess the animation's gone. Just stay there.

For the classic PKU cases, both variants and the diplotype were most often pathogenic. Interestingly, even in classic PKU, 11 cases, that is roughly 15% of them, had one of the variants as a variant of uncertain significance. And among the MS/MS false positive cases with two variants, approximately one-third of them had two variants in the diplotype annotated as pathogenic. Next, please.

For common variants, we can create maps connecting the two variants to the phenotype. The center ring is colored by the pathogenicity of the variant. The second ring is divided into segments for individuals and shaded by the second variant pathogenicity. The outer ring represents the phenotype and is shaded accordingly. The naive view is represented by the plot on the lower right. Two pathogenic variants produced classic PKU. The upper left diagram shows the complexity of the situation. Even though both variants are called pathogenic, the result is mild or no disease. Next, please.

Sequencing for screening, in effect, reverses the process of diagnostic sequencing. Rather than identifying the genetic cause of an existing phenotype, screening seeks to infer a future phenotype from the existing genetic variants. In this study, roughly one-third of the variants had not been seen before, so it was hard to make inferences. The difficulty was increased by the ethnic diversity of the California population. Inferences about disease severity from pathogenicity assertions of individual variants in autosomal recessive disorders are not straightforward. Next, please. Next.

A feature of the NSIGHT program was an important integrated ESLI program. The NBC group convened the NSIGHT Ethics and Policy Advisory Board, including representatives from all four of the NSIGHT groups plus other experts in law, ethics, law, policy, and medicine. The group considered four contexts in which genetic sequencing might be applied to newborns. One, clinical care of sick infants, particularly in the NICU; two, public health newborn screening; three, routine pediatric care of healthy newborns; and four, direct to consumer genetic testing. Next, please.

The conclusion of the deliberations can be summarized by the title of the final report,

Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies. Next, please.

In summary, at this time, WES alone is not suitable as a sole screening methodology for inborn errors of metabolism. For selected disorders, sequencing was as good as MS/MS and sequence information could reduce false positive results and could facilitate an accurate and timely case resolution. For any project like this, it takes a large team to accomplish the goals. I would like to express my thanks to them all and my pleasure at being included in the group. We want to thank our funders at NHGRI and NICHD for their ongoing encouragement during the course of the project. Thank you.

>> CYNTHIA POWELL: Thank you, Dr. Currier.

Our next speaker will be Dr. Kingsmore. It looks like your slides are up and ready.

>> STEPHEN KINGSMORE: Thank you, Cynthia. Thank you for this opportunity to talk to you all. I'm pretty excited to do so.

So I'm going to emphasize two points in terms of this committee's charter. The first is technical information to develop heritable disorders program priorities. I'm going to focus on that technical information to help you develop heritable disorders program priorities. The second theme will be another of your charter recommendations, which is recommendations to reduce morbidity and mortality from heritable disorders in newborns and children. So I'm going to talk about newborns and children who are suffering with symptoms in an intensive care unit setting with disorders that are suggestive of a heritable disorder. Next slide. Next slide. Next slide. Thank you.

Okay. So three factors are coalescing right now to revolutionize the approach to diagnosis and screening. The first one is the exponential decrease in the cost of genome sequencing, which stands now at roughly $600 to $700 for a genome sequence. Next slide, please.

The second one is something which this program did, the NSIGHT program at our site, which was a desire to make clinical genome sequencing be relevant in terms of the timeliness aspect of newborn screening. Could we indeed return results in two days as is necessary for unstable children with suspected heritable disorders? The good news is that during the period of award, we were able to reduce the time to result and to move that into a production phase. What you see there in the orange dots are various times in which we could make a diagnosis, that's time from dried blood spot to diagnosis and issuing a verbal provisional report. And the new benchmark, which isn't actually yet published, is about 13.5 hours. What that translates to in a production environment is that we can certainly meet that two-day turnaround time with a clinical whole genomic sequence. Next slide.

This is the current pipeline. This is a little bit technical but let me walk you through it. We start off with a typical punch or couple of punches from a dried blood spot. We have done this again with the same resource that Robert Currier mentioned in his presentation. It is archived California dried blood spots dating back in some cases to 20 years old. So what we've done is to validate that they indeed can generate a high-quality clinical genome sequence. For most of the work that we're doing, we're getting consent in phlebotomy and actually building those dried blood spots on the spot in the intensive care unit. As I say, we've done this on archived samples. The first step is to get the DNA ready for genome sequencing, and that is not possible in 80 minutes. There is a new prep that both involves DNA extraction and library preparation as a single automated protocol with minimal hands-on time by a laboratory specialist. We then run the genome sequencing to about 100 nucleotides. It's really the identical protocol to an exome. It's just that we have stripped away the exome steps, so we put the library immediately onto a sequencer. And using the latest generation of alumina instruments, recipes, and flosses,

we can now complete genome sequencing in less than 12 hours. We then use another alumina technology, the dragon platform, which uses hyper threading to greatly expedite the computational side of the genome-wide variant column. This currently takes about 45 minutes. It really scales with the full genome coverage. So a 30X genome would take 30 minutes. A 45X genome will take 45 minutes. In addition, since most of our children are actually in an intensive care unit and have a medical record, it has useful information in terms of narrowing the differential diagnosis. We use natural language processing to extract from nonstructured text the clinical features that summarize a child's illness. On average, we wind up with somewhere like 80 to 250 clinical features describing that child's illness. That's the clinic think electronic health record natural language processing step. Finally, during the period of award, we have prototyped and clinically validated now the use of artificial intelligence to take those two inputs, roughly five million genomic variants and 150 clinical features, and parsed that against approximately 6,000 genetic diseases and to do so in about ten minutes and provide for a lab director inspection and automated provisional diagnosis. This is the state of play right now today in terms of what's possible with whole genome sequencing. It may be surprising to you, but it really, I think, underscores that this technology increasingly is ready for the sickest of patients in hospitals, but also is ready for consideration technically, at any rate, from the newborn screening perspective. Next slide.

One thing -- let's just take a quick look at that. One thing which Jonathan had mentioned was the analytic performance. For a long time, maybe five years, we've known that the analytic performance for single nucleotide variants of next generation sequencing, whether exome sequencing or genome sequencing, was best in class, precision and recall of 99.9%, better than, say, traditional methods of genotyping. But more recently, using this dragon technology and genome in a bottle samples, we have been able to improve its capabilities for other variant calls. Really, it's not also best in class for short insertion/deletion nucleotide variants, and also for structural variants and copy number variants. These precision and recall numbers may not seem perfect to you, and they're not, but they are substantially better than microarray, which is the gold standard technology currently in use. Really, in terms of clinical diagnostics, this now is the platform of choice. Next slide.

So I mentioned this briefly that these are the timeliness goals that you're aiming for with newborn screening. And there's two of them, not one. So we actually have built two flavors of rapid genome sequencing, one called rapid or R and the other called ultra-rapid. They really correspond to those two types of conditions, the time critical conditions and the other conditions. And I don't think there's any doubt that rapid whole genome sequencing meets the timeliness goals at this juncture. Next slide.

This just underscores what I've showed you. This is actually production. So this is a production environment without all the bells and whistles that I have shown you in terms of some of the newer technologies. And you can see that last month, October, our median turnaround time in the ultra-rapid was 30 hours in clinical production. That's before we have implemented a number of those very new features that underpin a 13.5-hour genome. We can anticipate that this graph over the next year will continue to decline pretty rapidly down towards less than 24 hours. Next slide.

So a bit like the others, this was a huge project. And I can't review all of our results. I'm going to review one clinical trial, so-called NSIGHT 2 clinical trial. It was a randomized control trial of 213 infants in neonatal intensive care units. There was the odd infant who was in the PICU or the CVICU, but most were in the regional NICU. Could you just click again, please? We have got some builds here. The experimental design is shown there, 213 infants in an ICU with a critical illness of unknown etiology at the time of admission. We purposefully limited enrollment to the first 96 hours of admission. Our goal here is to have genome sequencing be done as a first-tier test to minimize that window of abbreviated empirical treatment and to be

able to treat disorders where disease progression occurs very rapidly, such as certain infantile encephalopathies. The methods are what I've just shown you. Now we are looking at the results which are summarized -- are a summary of three different articles in American Journal of Human Genetics which are shown there.

First of all, our diagnostic rates varied depending on the modality. It was 21% for rapid genome or exome. It was 46 percent for ultra-rapid because there's different selection criteria in those two groups. And those positive results were returned in the median of two days. So we then had physician questionnaires and parental questionnaires in terms of how useful is this information. Does it change management? Does it change outcomes? And what you can see is the answer is yes. For the vast majority of positive results, it changes management and dramatically, in 39%, it changed outcome according to physician perception. When it came to parental perceptions, and this ties into the ethical, legal, and social implement -- implications of research that my coinvestigators have spoken about, we were keen to get parental perspectives. There they were even more black and white, where there was no concern -- there was no realized concern in terms of anxiety or depression as a result of returning genomic results in an ICU setting in a newborn. Could you click on the next two, please?

What was very much surprising for us -- sorry, just back up. Thank you. However, was the utility of negative results. Genome is very different than a screen for selected conditions. It's very different from an exome. Because we are decoding the entire genome, we can actually scan the entire gene region, introns and exons, and, in many cases, can rule out specific differentials. And this, therefore, has huge negative predictive value in terms of physician perception of whether the case, the child, has a genetic disease. And so 72% of clinicians reported that negative results had clinical utility. In 16%, it changed outcome. Sorry. In 16%, it changed clinical management during the NICU stay. And in 8%, it changed outcome. When it came to parents, again, it was more black and white. What we found, to put it in layman's terms, is that they report that we had ruled out the genetic disorders on the differential diagnosis list was very good news to most parents and did, indeed, change in many instances some of their decision-making in terms of care intensity. Next slide.

So putting this in perspective, when this work was started, there was very little evidence for what I've just shown you. Now there is quite a bit of evidence. There are 19 published studies. And the weighted average, as you can see at the bottom, really fits quite well with what I just showed you in the NSIGHT study. Certainly, what we found was not an outlier, that across 1,600 patients, about a third get a diagnosis, a little bit over a quarter we have a change in utility or clinical utility for the results. I would say that the study I've shown you is the only one really yet to look in detail at negative results and their clinical utility. And we have substantial changes in outcome. Next slide.

So I'm going to talk just in the last couple of slides about where we're at in terms of global implementation. This technology, as you know, was born in the U.S. The first studies were done in the U.S., but other countries with public health systems are able to make policy decisions faster than us with our federated system. And so, in fact, it's not policy. In Wales and England for children who are in-patients and have diseases of unknown etiology to get a rapid genome sequencing test, that's now a policy decision in the National Health Service in both of those countries. Australia started out with rapid exomes, but more recently they have moved also to rapid genomes and they are also in the implementation phase nationally in terms of having this be available for all in-patient infants who have diseases of unknown etiology. In the U.S., we have lagged a bit behind. Right now, I'm showing you the sites that we know of who are doing rapid genome sequencing in intensive care units. There's 58 of them currently. But I want to focus in on the three state projects because these are really public health projects. In each case, these are implementation studies. They're not really search studies. So they're being performed as quality improvement projects without consent. And there are three of them. There's project

Baby Deer in Michigan, Baby Manatee in Florida, and Baby Bear in California. I'll show you the results of the latter since it's now complete. Next slide.

There were five participating sites. We enrolled 183 infants. It covered all of the geographies and ethnicities of our very diverse state. And the intent in this study was to explore clinical utility and economic value in Medicare newborns. Next slide.

The diagnosis rate was similar to the studies I've shown you, all told, 43%. The proportion who had a change in care also was similar to the previous studies, 31%, and time to result is a bit cut off. I apologize. The median turnaround time was three days in terms of time to result. Next slide. Just one more click, please.

Two slides on the cost impact. The first on the left shows cost effectiveness modeling in the patients and we stratified this according to time to result. This is essentially a sensitivity analysis. The actual time to result was three days, but we modeled a 7 and a 14-day turnaround time. What we found was that there were significant cost savings both for the hospitals and for Medicare with a three-day turnaround time, but that it was about breakeven with 7-day turnaround time and net cost additive for 14-day turnaround time. More recently, we have started to model ongoing cost of care. We're still modeling this data. But what we are finding, which should be no surprise, is that the cost savings are not limited to that initial hospitalization, but they continue to accrue in the out years. We will need our population to grow a little bit to model this more fully. But net and aggregate, the message is quite clear across this and our three other studies that this is net cost savings for Medicare. Next slide.

Baby Manatee, I don't have time to go into it, but similar findings. And I think one more click has the cost savings. I don't really have time to go into this, but a similar approach and a similar result. The modeling was done somewhat differently from us. Next slide.

So wrapping up, we believe that the Wilson-Jungner criteria can be applied to newborn screening by whole genome sequencing. Obviously, there are quite a few changes. It becomes allele driven rather than disorder driven. And as with traditional newborn screening, we need an entire system of delivery and that they focus solely on just the diagnostic piece where the screening piece will not be sufficient. We need a strong focus on immediate implementation of interventions. So as part of this, we have focused on developing a list, as has Genome England, of disorders that could be piloted for newborn screening using whole genome sequencing. The British started before us. But thanks to COVID, they are now behind us in terms of their planning. We have identified about 500 conditions that we feel sort of kind of meet the criteria. We haven't done the type of in-depth analysis that this committee would require for a recommendation. But we focused in on those and we are now preparing for each of those, the equivalent of action sheets, in terms of what are those indicated interventions and are we certain that they would, indeed, change the outcome in these conditions. Next slide.

This shows one of the pages, a condition that we have diagnosed in one individual, Timothy syndrome. This normally presents a sudden infant death syndrome. But if you can pick it up in a child before they have a ventricular tachydysrhythmia, then it's imminently treatable initially with propranolol. We then proceed to add mexiletine. And if you have dysrhythmias despite those two medications, you add an AICD, an implantable defibrillator which can now be done in infants, and you may also need a pacemaker. And I think that was my last slide.

Sorry, summary. Rapid and ultra-rapid genome sequencing is now being widely adopted for infants and children with heritable disorders. Albeit, sadly, we are losing the race to other first-world countries. The current application for which the evidence pretty strongly supports these in-patient infants and children with diseases with unknown etiology. That's a very broad bin, as you can imagine. All different types of conditions, neurologic, metabolic, pretty much

every other organ system is included. We do believe that the technology at this juncture -- this was not true when we started the NSIGHT project, but we do feel that now, thanks in large measure to the NSIGHT study, it is possible to foresee adaptation of the technology to provide newborn screening for disorders that meet the criteria and that it might be possible within the next few years to see the cost of operating that within the realm of what might potentially be feasible.

Thank you very much.

>> CYNTHIA POWELL: Thank you, Dr. Kingsmore.

Our last speaker will be Dr. Robert Green.

>> ROBERT GREEN: All right. Thank you very much, everybody. It's a pleasure to be here. Appreciate the invitation. Great to see the NSIGHT band back together again. And really enjoying seeing the previous presentations as the data has been analyzed and presented.

I'll be speaking on BabySeq project and I'll be focusing on the sequencing of healthy newborns and how this may relate to a more global change in the healthcare system towards preventive genomics. Next slide, please.

I want to indicate my support and disclosures which you see there. I'm compensated for advisory services to the companies you see there. As was mentioned at the beginning, I cofounded a tele-genomics company called Genome Medical. Next slide, please.

So we've been trying to focus on translational genomics, like many of the previous speakers. Really, this comes down to costs, risks, and benefits, particularly if you're talking about screening, which I've become convinced that we are and we need to go ahead and use the language of screening when we're talking about newborn sequencing. However, I have always thought of it as different from newborn, the -- just for the record, I want to say that everything I'm talking about is going to be speaking about voluntary screening of newborns at this moment in time. Nothing related to required. Next slide, please.

We do have a suite of research programs, and this BabySeq fits into them. A lot of the work I'm going to be presenting has sort of evolved through these different programs. The major ones you see in the large type, and the smaller ones where we're playing a supportive role in the smaller type. Next slide.

And also, like everyone else, I want to acknowledge this wonderful team of the BabySeq project, particularly Allen Beggs, with whom I was the MPI for this project, and we led it together every step of the way. You can also see Heidi Rehm, Kurt Christiansen, Ingrid Holme, and Amy who have supported us, senior people supporting us throughout, Amy McGuire. Next slide, please.

So we designed this from the beginning as a randomized trial. Now, it really had two parts. We actually started off with a randomized trial of newborns in the ICU. But unlike Stephen's work, we didn't select for babies that would be most likely to benefit from sequencing. We were very curious as to whether if you sequenced all-comers, you would find unanticipated information. And the answer, at least in the small sample size that we had, was no, that is not a good idea. Stephen is right. You should really focus on the people for whom you can carve out that indication-based thing. We just didn't find enough in sort of a random selection of NICU babies. So I'm going to concentrate mostly on the right side of this, which was our randomized trial of healthy newborns. Next slide.

Some of the decisions we made early on were that we were going to look initially at childhood onset, but that included adolescence. It cast a broad net. We were going to look at the disease gene associations that had strong or moderate evidence. We were going to look primarily at those with high or moderate penetrants -- we defined all these as best we could -- and that were somewhat actionable in childhood, although we cast a very broad net for what actionable meant. Later on, we added a very limited number of adult-onset conditions, mostly associated with the ACMG59. From the very beginning, I think this has really been the case throughout most people who are trying to screen with genomics, we only reported pathogenic and likely pathogenic variants. If there was not an indication for this, we simply did not report variants of uncertain significance. The history of VUS', I think, supports this because they often get reclassified. When they're reclassified, they are predominantly, not exclusively, but predominantly reclassified in a benign direction. Next slide, please. Go ahead and click so we get through the animation, but right there. One back. Thanks.

Like, I guess, Stephen was describing, I didn't realize, Stephen, you were making a list. We have been trying to make a list because although you can do all 20,000 genes, you can do all 68,000 genes ever been associated in the literature with human disease, if you're screening, as Jonathan pointed out, you really have a responsibility to focus on strong disease gene associations. And so this shows you how we first took about 1,500 genes, separated out the ones we felt had strong and definitive evidence, then further separated out the ones we felt had high or moderate penetrants, and the ones that we felt had some aspect of age of onset below the age of 18. And then you can see over on the right how that broke down, finally, into 954 genes that met our reporting criteria. This became the BabySeq list. Other countries have been very curious about this because you can certainly disagree with our precepts, but there was a very logical, rational way we chose to try to develop the list. Next slide, please.

Now, the demographics of our enrolled parents were primarily white and primarily non-Hispanic -- if you go onto the next slide -- but not exclusively so. This is an interesting slide. When we published this, it got widely interpreted to mean nobody wants healthy genome sequencing for their babies. I don't really see it that way. As Jonathan said, it's a really tough time to approach people, as we did, on the newborn unit in the 24 hours after they've just had a baby. You know, conventional newborn screening, their baby is just whisked away, the heel stick is done. More than half of the time, as I understand, people don't even remember that it got done. For this, we had to go through a consent process. It was rather lengthy. And we actually required a blood draw. Nobody wanted their newborn baby stuck. There were a lot of people who said, first of all, I'm not interested in any research, go away, I'm exhausted, or just didn't give us a reason. But then when we sat down and talked to people about the reasons for which they were disinterested, you can see that privacy and discrimination was very high on the list, a few people were frightened about returned results, but most people, if you were going to pick one reason, were concerned about the study logistics because we were on a big regional newborn birthing unit and people had to come back in in-person for our protocol. I will say that of the people who agreed to sit down with us and hear a description of the study, 60% went ahead and agreed. So this is an interesting ascertainment bias question. Not for a single study do we go door to door in the United States and try to recruit every single person. We always have some sort of prescreening, pre-ascertainment going on, whether they're already a patient with us, a patient in our healthcare system, a member of a biobank, picked us out of a newspaper, advertisement, or something. Next slide, please.

Here's the medical part of what we found. When we looked at that many genes -- of course, the more genes you look at, the more findings -- and you look at likely pathogenic and pathogenic only, we found 11% of our ostensibly healthy babies had an unanticipated monogenic, by that, we mean a dominant heterozygote or a biallelic recessive set of findings. There they are. What was fascinating is for about a quarter of them, when we circled around, in light of the DNA evidence and reexamined the child, for the top four there, we found evidence

that the condition in question was already underway, that there was already an abnormality. In another set of five individuals, when we circled back, we found family history that had not been reported the first time that a genetic counselor had taken a gold standard family history. And then for the remaining ones, of course, that's the ones people are so worried about because that's the sort of thing these babies are now living their life with their parents having the knowledge that they are at risk for one or another of these conditions. But 11% was quite a lot higher than, I think, most people would have imagined. Not as high as what we found in MedSeq where we didn't set any limits on actionability. We didn't set any limits on adult-onset or childhood-onset. We only reported on close to 4,000 genes that we felt had good penetrants and good disease gene association. There, it was 20%. So I think one of the things that's pretty remarkable about this, and you might disagree, is that there are more people walking around with genetic risk factors for monogenetic disease than we ever thought were out there. There has been since a number of studies that have supported these numbers. Next slide, please.

In terms of recessive carrier traits, again, we looked at a number in the gene list that we had. And of the ones that we looked at, I think it was 566 genes, 88% of infants had at least one carrier. You might think, well, is that even important? But it was really interesting to the parents of reproductive age because most of the time they had no idea they were carrying this. Actually, in one of the babies, and we only had 159 babies in the sequencing arm, in one of the babies, the parents acted on this where they found a heterozygote, unaffected recessive carrier in the baby, they checked each other, and it turned out that the other parent was a carrier, too. And they went ahead to use reproductive technologies for their next baby. I guess the point here is there is, again, an awful lot of information here that neither standard prenatal care nor any of the commercial panels are picking up in terms of what's there in these ostensibly healthy newborn babies. Next slide.

And although we don't have anything like the numbers that Rob presented from California, we did just kind of look in our own small cohort at the association between what we found sequencing and what we found on newborn screening. This was sort of conflated by the bottom right where there were seven NICU babies where there were abnormalities that did not turn out to be true. What was interesting is the only thing that showed up both on our little sample was Biotinidase deficiency. You can see the whole left column under sequencing positive, there were quite bit of findings in the sequencing column that turned out to be present, even though they weren't, of course, alluded to on newborn screening, conventional newborn screening. Next slide.

Now, the beauty of a randomized trial is that you are actually selecting for people who wanted to get sequenced and then they got disappointed, but it makes it very easy and rigorous to measure particularly the kind of short-term risks that everyone is concerned about. So here's a snapshot of looking at depression, anxiety, self-blame, or some sort of interference that the parent could report all on standardized scales in terms of their relationship with the baby, and you can see that not only did the groups not reach any kind of clinical cut-offs, but that there were no differences between the control group, the entire group that got exome sequenced, and the gray boxes, which are the smaller group, that learned they were carrying a monogenic disease risk. Next slide.

Not to belabor this, but we did the same thing with validated scales of parent-child bonding disruption or child vulnerability, according to the parents. And similarly, the scores were below the cut-offs, and they were not significantly different from each other in terms of the randomization. Next slide.

We spent quite a lot of effort on trying to assess the downstream medical impact. Of 17 newborns with unanticipated genomic findings, there were 43 services ordered. Those broke down into 23 specialty visits and 20 other resources. And these were, of course, mostly things

that were not happening in the control group. Next slide.

But we could look at specifics for spending. Although the spending in the sequenced babies was higher, interestingly enough, at least with our small sample size and the wide range that we found, although the means were different, these differences are not statistically significantly different. So I think we'll need a larger sample size to really address whether this is truly going to be the kind of cost concern that so many people are worried about in the screening situation. Next slide.

We're using some of these data to model these out because what you'd really like to know is if you sequence a baby at birth and you get everything that you can get, a little bit differently than Jonathan's vision of sort of re-interrogating over the lifespan, what could you learn that could save you morbidity, mortality, and even cost at every step in the developmental pipeline. Next slide.

So I'll just mention that a variety of our studies have shown that there is quite a lot in the genome. We're not going to talk today about polygenics or pharmacogenomics, but our studies, plus several others, again, I just think support the thesis that there is a lot of risk information in the genome that may be worth knowing, whether you're an infant or you're an adult. Next slide.

I'll stop there. Again, this was a privilege to work with this group and really thank the child institute and NHGRI for the funding. I think that I would leave you with just some sensitivity to a couple of terms. I hope I'm not misquoting you, Jonathan, but I hear you say diagnose a lot, even when we're talking about DNA first, and I would really reframe that differently as risk stratification. It still has problems in terms of the cost-benefit of screening, but it's really misleading, and I think it speaks to the ways in which we came to genomics through diagnostic testing to conflate this with diagnosis. This is not diagnosis when these are obviously healthy people, many of whom are never going to get the disease. Dr. Currier, even you, you said something about inferring a future phenotype. That's closer, because part of the question is what is the probability that someone is going to get this condition or a precursor to this condition or a subclinical or previously unrecognized component of this condition in a certain timeframe or across their entire life?

So I think that's where we're heading, and those are really difficult questions to answer in an experimental form, but I think that's the challenge that lies before us. Thank you very much.

>> CYNTHIA POWELL: Thank you, Dr. Green. We'll now open it up to questions or comments from first committee members and then our organizational representatives. Thank you again to our four speakers today. As a reminder, please unmute yourself and state your first and last names. Just to get us started, I'd like to ask Dr. Currier, Bob, your data is pretty clear that sequencing would not be a good substitution as a first tier test for inborn errors of metabolism, but what are your thoughts about its use potentially as a second or third tier test, specifically to essential cut down on false positive results?

>> ROBERT CURRIER: Robert Currier. I think there's a lot of potential for that, particularly -- well, for two reasons. One, because the number of people who would need a second-tier test after primary MS/MS screening is much smaller than the whole population, so it makes the economic impact smaller. And with the data from Dr. Kingsmore about the possibility rapid turnaround, it suggests that even in time-critical disorders, a DNA-based second tier test might be really effective if it could be essentially implemented immediately in the screening workflow.

>> CYNTHIA POWELL: Thank you. Mei Baker.

>> MEI BAKER: Hi. Mei Baker, committee member. Thank you for the whole panel. That's a really good talk. A lot of questions for sure. But before I go on my question, I want to follow up with the question talked about a second tier. I often said that I don't think I got enough attention, so I'm going to mention it here again. So talk about a second tier in newborn screening setting, how many times one newborn will have five or ten different screenings positives? In that situation, it's a false positive. Why we next gen sequencing? Whole genome to a second tier? I think it just poses a question people can think about. Why, when we started doing the Pompe, we end up with deciding to do -- if the GAA low on one sample, I can't wait for another 10 or 20 samples to do my second tier. You have to do it right away. So I just pose the question here.

And my question, I have several questions, but I'm trying to be mindful of time, a couple for Dr. Kingsmore. You talk about the turnaround time. I'm wondering, in your thinking, have you thought about through put? Even you have multiple studies. You talk about hundreds. The newborn screening setting where I work in Wisconsin, it's a medium or small state. Every day, we have 300 to 500 samples, and it's not just one day. You have Monday have this, Tuesday, Thursday, and Friday. So how does the through put been taken into the consideration?

Another thing I want quick before you answer is I just want to be sure I catch it right because you talk about cost and talk about 500 for genome. So that's the base on the coverage on the 30X? Am I right? Thank you. So if you can respond to my question, that would be great.

>> STEPHEN KINGSMORE: Thank you. Good questions. First of all, in terms of secondary testing, one application area that we found a lot of traction in immune deficiency disorders where a myriad of tests are often performed to figure out what's the molecular diagnosis that causes an abnormal T cell excision circle result. And the clock is ticking on those kids. They need to be moved into transplant or not or gene therapy or factor supplementation. So that's a good example where I think a genomic approach makes a ton of sense.

In terms of through put, your question is excellent. This is an area that's moving pretty fast. We now are seeing studies of half a million to a million being done in specific populations, most notably Genome England with their half million cases. The technology has changed quite dramatically. Another instrument with the S4 flow cell, for example, will run 48 genomes per run per instrument.

Your point is well taken that scalability to 4 million is still some way off. I wouldn't want to suggest to the committee now is the time to do this. I think now is a good time to be thinking about recommending a pilot study, knowing that some of the trends I've shown you are not going to stop. They're going to continue this pace of change. And probably in a two- to five-year timeframe, I think we'll be in a good space.

Yes, you're right. It was a 30X research genome. Again, I wouldn't want to mislead the committee in terms of cost. I don't believe genome sequencing would fit the types of costs that the public health system can support yet, but I am watching that curve and it is continuing to drop. So at some point, we will get there, and nobody can quite predict when. Thank you.

>> CYNTHIA POWELL: Thank you. Next, Melissa Parisi.

>> MELISSA PARISI: Thank you. This is Melissa Parisi from NICHD. I just want to thank all four of the presenters and the entire teams that you all represent with regard to the quality of the presentations and the summary of your conclusions.

When we embarked upon this program now almost a decade ago when we were just

starting to think about the NSIGHT projects and how to even conceive of sequencing in newborns, you know, at that time, it wasn't even feasible to be doing whole genome sequencing on dried blood spots. The technology has changed dramatically. And I think the projects each of them has had has made several contributions in this arena, and each of which was unique in its characterization and its goals.

My question for you all is one that's maybe a little more hypothetical and sort of pie in the sky in a sense. And I guess I would ask each of the four project leads if you -- either one of two things. If you had to do it over again, what would you have done differently when you put these projects together and/or what do you think is the next logical step for this type of inquiry with regard to sequencing, and I want to keep it broad, sequencing in newborns, because I know that the paradigms of sequencing in the newborn screening arena has its challenges, as has been pointed out by a number of you all in your presentations. I'm asking a little bit more of a hypothetical question about what you would either have done differently or what you see is the next step for this type of line of inquiry. Thank you.

>> CYNTHIA POWELL: Maybe take in order. Jonathan, do you want to go first?

>> JONATHAN BERG: Yeah, sure. So I think I would have written the RFA differently. We were forced to use an exome or genome approach by the RFA. That was the point of the RFA is to investigate genome sequencing. First, it's the NHGRI that is really behind whole genome sequencing. That's their test of choice. For most clinicians, you know, you don't always hit everything with a sledgehammer. Sometimes you actually want to use a fine chisel or, you know, a very small screwdriver. A genome can be like a sledgehammer sometimes. I'm very much into people thinking outside of that box at targeted sequencing, which can gain some of the same economies of scale by multiplexing that you can through whole genome sequencing. You just simply aren't sequencing the irrelevant parts of the genome that you don't need to know for whatever purpose you are sequencing. I would actually advocate that we pursue more research in targeted sequencing. I think that was the conclusion of my talk.

I just want to take one second, if I can, to respond to something that Robert said at the end. Robert, you, I think, mischaracterized a little bit of what I said. A diagnosis is a diagnosis. The reason it's a diagnosis is you have to do something about it. You could just watch and wait if you diagnose someone with a Mendelian disorder and wait to see if they develop symptoms and then treat them for them. You could decide that the best thing to do is to do something preemptive, in which you are treating them in advance of symptoms developing. And that preemptive treatment might be a surgery. It might be removing a body part. It might be a stem cell transplant. And so the very fact that you make a diagnosis that is a molecular diagnosis, that then puts the patient onto a path for management says that you are making a diagnosis. And so I actually reject your statement that we are not making a diagnosis. For Mendelian disorders, yes, we are saying if I find an MLH1 pathogenic variant in a baby, that they are at risk to develop the systems of Lynch syndrome. We're going to treat them as though they have Lynch syndrome and we're going to start them with early screening. For the child or infant, they're not going to do anything until they become an adult, so that's irrelevant information for the next 20 to 25 years.

>> ROBERT GREEN: You're running out the clock here because I want to be able to respond.

>> JONATHAN NBERG: But the point here, Robert, is these are diagnoses that we are making molecularly and that we are acting on. That's the point. That's a molecular diagnosis.

>> ROBERT GREEN: Should I go next, Cynthia?

>> CYNTHIA POWELL: No. We're going to do it in order of presentations. Bob Currier.

>> ROBERT CURRIER: Sorry. I think my -- I'll just focus on this question of it's essentially related to what Jonathan was just saying. To what extent is a molecular diagnosis a diagnosis? And I think that there is a place for a lot more substantial research into -- more subtle research about when are variants pathogenic in combination, that really it's -- what we need to start thinking about is pathogenicity for diplotypes for Mendelian recessive disorders. In CF, if you have a 508F deletion that's homozygous, you can go ahead and start treating, even though the Cystic Fibrosis Foundation wants you to do a sweat test before it is a diagnosis. That's because CFPR has been studied more intensively than most genes, so we know what's going on, even though we don't always.

>> CYNTHIA POWELL: Stephen Kingsmore.

>> STEPHEN KINGSMORE: Very briefly. I think that the RFA was stunningly adventurous. I think I have not seen anything come out of NIH that is been quite so cutting or bleeding edge as this ever. I don't think I ever will again. I think you are to be hugely congratulated for a very forward looking RFA. I can't think of a way that it could conceivably have been done better given the complete absence of knowledge that we had when this started, and we all skated along a learning curve and we all wound up in places we could never have anticipated.

My biggest regret, obviously, is that it was only at the end of the award that we really knew the right experimental designs. Sadly, we didn't have a follow-on project. Now I think we really are powered to do the next logical step and to result in something that we can bring to this committee as a pilot project that would seek their recommendations.

>> CYNTHIA POWELL: Now Robert Green.

>> ROBERT GREEN: Okay, thanks. The only thing I really would have done differently -- I thought the RFA was amazing. The only thing I would have done differently would be to drop the NICU hypothesis from the beginning because it obviously was wrong. But we were pretty excited about how things turned out for us. You know, only wish we could do bigger sample size, could streamline the logistics of both analysis and recruitment. And we are hoping we have a grant under review now that looks like it has a favorable score from MCAT. We are hoping to, in fact, exactly do that, expand with an emphasize on underrepresented minorities as well as the folks that usually sign up for such projects. So we're very excited about expanding on BabySeq.

You know, Jonathan, I so admire you and your work, but I reject your rejection. I think that a diagnosis is by no means the same thing as a risk factor. And I think that is sort of the fundamental narrative flaw that is preventing us from moving genomics into the day-to-day practice of medicine and if we can reconceptualize genomics as risk stratification. I do agree with you we don't always know what to do yet. And I do agree with you that if we react foolishly, we will waste resources and can even harm people. The history of screening has demonstrated that without question. So I hope I'm not a Pollyanna here. But if we carefully choose what we want to screen and we carefully titrate what we do afterwards rather than react as if it were a diagnosis, then I think we have an opportunity to really make a public health difference.

>> CYNTHIA POWELL: Great. Thank you. I'm going to take the questions from the next three individuals who now have their hands raised. So first is Georgianne Arnold.

>> GEORGIANNE ARNOLD: This is for Dr. Green. On the slide you presented with the 10% of patients who turned out to have a Mendelian disorder, what was the denominator in that

again? Can you remind me?

>> ROBERT GREEN: Yes. It was 159 people who were exome sequenced, and about 900 genes that were looked at, both dominant and recessive. Of those, 11% had a -- we specifically used, because of the discussion we have just been having, Georgianne, that we specifically used term monogenetic disease risk, MDR, and 11% had that. That was either a dominant mutation or biallelic recessive.

>> GEORGIANNE ARNOLD: I forgot to introduce myself. I'm with Society of Inherited Metabolic Disorders. Those 157 were sequenced randomly from the NICU?

>> ROBERT GREEN: No. No. Those 159 represent the folks in our study who were sequenced in the entire study, a small number of NICU babies for which we did not find any diagnostic cause. And so all of those findings were what I'm calling unanticipated findings. They were not -- they were not the answer to why they were in the NICU. They were mostly healthy babies who had nothing wrong with them. So 159 babies, 11% unanticipated monogenic risk discoveries.

>> GEORGIANNE ARNOLD: Okay. Thank you. One more quick question. Sorry. So, 150 years ago, when I was starting out in genetics, the estimates were that we all carry five to seven recessive genes. Is that being held out with genomics?

>> ROBERT GREEN: Yes. We had a slide that we didn't show. Other people have done even larger numbers that showed that, on average, people had about two and babies had between one and eight recessive carriers.

>> GEORGIANNE ARNOLD: THANK YOU.

>> CYNTHIA POWELL: Scott Grosse?

>> SCOTT GROSSE: Thank you. For Dr. Green. I think the Biotinidase deficiency case that was identified indicates some of the ambiguity and clinical diagnosis in public health criteria may not align. I believe that was a partial Biotinidase deficiency case. Many states do not consider that to meet the newborn screening criteria. Would you care to respond?

>> ROBERT GREEN: You're absolutely right. We wrote an entire paper on that one case because it was picked up by newborn screening. The newborn screening was repeated that was normal. We picked up the mutations through that circumstance. We called in an expert and got enzyme levels that were, like, 40% of normal. Nobody knew, including the expert, whether 40% of normal was going to cause some IQ points or something else. Baby got started on a vitamin biotin and, of course, is doing well. Might have been doing well without any intervention whatsoever. Hard to tell. But that just really brings home how difficult this is. I can tell you we haven't claimed credit for solving that baby. We've been honest every step of the way that that baby might have done well anyway. Family totally understands that, but they're very grateful to know what they know.

>> CYNTHIA POWELL: Max Muenke.

>> MAX MUENKE: I'm Max Muenke. I am the org representative for ACMG. I have a question for both Dr. Berg and Dr. Green. So I haven't started 150 years ago, but I've been in genetics for a long time. Long time. And I think the part that always has fascinated me was the part how do we counsel families for recurrence risk? And it kind of, without wanting to pour salt in the wounds of is it a diagnosis or is it something else. Actually, I enjoyed it tremendously, might I say. Most of all, I want to say I have enjoyed those talks tremendously. I have learned

from studying holoprosencephaly with the very first patient that I saw at Children's Hospital in Philadelphia in 1986 that there is an extreme variability within the same family with the identical mutation of variant, however we want to call it there. And so I wonder, is there anything that you have learned from your studies, published/unpublished, from these or other studies where you feel that eventually we will make a little better -- where we maybe come a little bit better predictors for predicting outcome in a planned pregnancy, even if there was a certain base change there that in another sibling goes together with a severe birth defect?

>> CYNTHIA POWELL: Robert?

>> ROBERT GREEN: Dr. Muenke, it's a privilege to hear your question. I don't know the answer. But I do think that we are changing from a world, as all you know, that we're changing from a world in which we rigorously see monogenic and polygenic commonly to a world where there is a spectrum. Almost everything that's monogenic has mediating factors that implied expressivity and penetrants along the way. It's really complicated. That's why I think -- it's one of the reasons why I think a risk factor modeling and mental modeling is better because we're gradually going to better understand not only the other genetic factors, like polygenic on top of monogenic, for example, which there is strong evidence suggesting that you're carrying the exact same monogenic variant. Your polygenic profile underneath that can put you at higher risk or lower risk than the average. But also, post a translational modification, metabolomics, the whole big data buzzsaw that we hear all the time will gradually give us insight into nuances. As we do so, ironically, I think it will be more complicated, but it will allow us to place genomics back in the day-to-day practice of medicine because we'll be dealing with probabilities, like we are with everything else, heart disease, diabetes, subsequent follow-up, and it should be material that all doctors are welcoming within their practice rather than this walled off city of overly sensitized information that gets claimed as our sandbox alone and then somehow doesn't get easily integrated into the day-to-day practice of medicine.

>> CYNTHIA POWELL: Jonathan.

>> JONATHAN BERG: I completely agree with Robert about the oversimplification of Mendelian versus polygenic. I've talked about that for a long time. The fact of the matter is we define, you know, pathogeny for a Mendelian disorder with a particular inheritance pattern, but there is a huge amount of variation in sort of the other factors that may define penetrants and expressivity. Until we have that understanding of all of the other genetic and non-genetic factors that we could pull into the sort of grand risk predictor, I think we are stuck in a, you know, Mendelian versus polygenic mindset, so that when we find a Mendelian variant that is pathogenic, or two, in a patient, that would be indicative of a genetic condition, then that's what compels us to act. Obviously, if we have better tools and better ways of refining risk prediction, particularly when we find them in asymptomatic people, that's just going to better serve to guide what we do for those patients. So I think that that's the vision -- there's just a huge amount of research that has to be done to really understand all of the modifiers. I think that's probably going to be the hardest task over the next few decades.

>> CYNTHIA POWELL: Mei, do you have one quick question or comment?

>> MEI BAKER: I'll be quick. One thing I want to follow up with the previous question for Dr. Kingsmore, and I agree with you. I think just leading me to say we have to think about continuity. We could have a single gene but have multiple -- very many mutations, for example, FTR2, which is right now, newborn screening programs does -- several do use the next gen sequencing to do the second tier.

I do have a question for Dr. Berg. When you in your end presentation you talk about sequencing and the newborn screen period time, some people may use over the time span, I

think I just want to ask from different angle, because according to Dr. Kingsmore, talk about the price getting lower and lower. And I just thinking the quality and the technology getting better and better. So one hand, you storage of the information maybe not perfect, and also, again, I use the through put population base, California, half a million a year, how many years you going to store them; right? And on the other hand, you can just do again when you need it. So could you comment on that?

>> JONATHAN BERG: So are you basically saying that one would return to the newborn blood spot to do sequencing over the years? Is that what you're suggesting?

>> MEI BAKER: No. I'm talking about, if I understand you correctly, because the information can utilize at a newborn screening period of time, but you have the raw data there, over the time span and go back and reanalyze it. Is it really cause-effect if I use term correctly? Is it just sequencing again when you need it?

>> JONATHAN BERG: Yeah. So the issue of whether it would be more cost-effective to sequence once and reanalyze that data for the next 20 to 25 years, or 50 to 80 years if you sequence a newborn, versus whether you're going to sequence again and again and again. And I think Stephen is probably the world's expert on how sequencing technology has evolved over time. And I think he would probably agree that he would rather sequence using the most up to date machines rather than the alumina machines from ten years ago. And so I think we are going to sequencing again. We're not going to be going back to the old stale data from five to ten years ago that was generated on a whole genome platform that was, you know, state of the art in 2015, but is not state of the art in 2020. And until that plateau happens, I think we will see people just sequencing again and not simply going back to the data from the sequencing test. It may be efficient to go to the data first and look to see if you find something and then re-sequence, sure. But I don't think that's necessarily the argument to say that all of this should be based on a whole genome sequence that's done at birth and that's the only time you're ever going to sequence that person. So from a cost standpoint, you know, it may be a little bit of an oversimplification to just calculate the cost of one genome once. I think we're going to be sequencing many, many times, many tissues. Right? And then there will be blood screening for somatic variation that happens and all sorts of things. So I actually think that we're going to look at a future where individuals have their genomes or parts of their genomes sequenced many times.

>> MEI BAKER: Thank you.

>> CYNTHIA POWELL: Thank you. Once again, I'd like to thank our four speakers. Thank you so much for participating and sharing all the information with the committee.

And finally, do any committee members have new business at this time? I'll give everyone a couple seconds to raise your hand if you have anything. Shawn, I see you waving your hand?

>> SHAWN MCCANDLESS: I was just waving at Stephen.

>> CYNTHIA POWELL: Oh, okay. All right. I don't see anything. So thank you all for participating in today's advisory committee meeting. The next meeting will be a webinar and is scheduled for February 11th and 12th of 2021. And unless there's any other comments, I will adjourn this December meeting.

Thank you. Stay safe, everyone. Stay healthy.

[Goodbyes].

Advisory Committee on Heritable Disorders In Newborns and Children

Meeting 12/1/2020

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