The Advisory Committee on Heritable Disorders in Newborns and Children

Day Two

HRSA Meeting

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C O N T E N T S

DAY 2

P R O C E E D I N G S

DR. JOSEPH A. BOCCHINI, JR.: If everyone will take their seats, we'll go ahead and get started. All right. So, welcome, everyone, to the second day of the August meeting of the Advisory Committee on Heritable Disorders in Newborns and Children. Today, we have a few more additional topics to present, and we're going to hear from the workgroups.

So, we're going to start with a roll call, so -- Kamila Mistry is on the phone today.

DR. KAMILA MISTRY: Yes, I'm here. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Okay. Mei Baker?

DR. MEI WANG BAKER: Here.

DR. JOSEPH A. BOCCHINI, JR.: I'm here. Jeff Brosco?

DR. JEFFREY P. BROSCO: Here.

DR. JOSEPH A. BOCCHINI, JR.: Carla Cuthbert?

DR. CARLA CUTHBERT: Here.

DR. JOSEPH A. BOCCHINI, JR.: Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH A. BOCCHINI, JR.: Michael Lu?

DR. MICHAEL LU: Here.

DR. JOSEPH A. BOCCHINI, JR.: Fred Lorey by phone?

DR. FRED LOREY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Dieter Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Beth Tarini by phone?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Cathy Wicklund?

DR. CATHERINE A. L. WICKLUND: Here.

DR. JOSEPH A. BOCCHINI, JR.: And Catharine Riley?

DR. CATHARINE RILEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: And for the organizational representatives, Robert Ostrander?

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH A. BOCCHINI, JR.: Michael Watson?

DR. MIKE WATSON: Here.

DR. JOSEPH A. BOCCHINI, JR.: Britton Rink?

DR. BRITTON RINK: Here.

DR. JOSEPH A. BOCCHINI, JR.: Kate Tullis?

DR. KATE TULLIS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Chris Kus?

DR. CHRIS KUS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Adam Kanis?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH A. BOCCHINI, JR.: Siobhan Doyle?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Cate Walsh Vockley?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: And Carol Greene?

DR. CAROL GREENE: Here.

DR. JOSEPH A. BOCCHINI, JR.: Thank you very much.

So -- Let's see, next slide -- So, first, we have someone rotating off the committee that I -- I'd like to mention a few things about -- And is Dr. Boyle on the line?

DR. COLEEN A. BOYLE: Yes, I am. Good morning.

DR. JOSEPH A. BOCCHINI, JR.: Good

morning, Colleen. We wanted to make mention of the fact that Dr. Colleen Boyle is rotating off the committee. She has been with the committee since it began, in 2004, and in fact, she served on the expert panel that developed the initial Uniform Screening Panel and was co-author on the "Newborn Screening: Toward a Uniform Screening Panel and System" newborn -- in -- report in 2006.

During her tenure on the committee, she's been involved as a co-author on a number of the papers that the committee has put out: co-author on the committee's report on "Advancing the Current Recommended Panel for Conditions for Newborn Screening," and a report on the "Methods for Evaluating Conditions Nominated for Population-Based Screening of Newborns and Children."

She led the Follow-Up and Treatment Subcommittee for many years, and it was under her leadership that this subcommittee, now workgroup, developed a number of reports and materials that

came through the committee for its approval.

In 2007, the workgroup developed the "Road Map to Implement Long-Term Follow-Up and Treatment in Newborn Screening," and in 2008, she co-authored the "Long-Term Follow-Up after Diagnosis" report, which was a statement by our committee on long-term follow-up after diagnosis of conditions through newborn screening. In 2012, she co-authored a manuscript on insurance coverage of medical foods for treatment of inherited metabolic disorders.

So, you can see from her -- her work that she's been involved with many of the important issues that this committee has tackled since its inception. And so, I -- I think it's very clear that she has contributed tremendously to the advancement of newborn -- newborn screening through her work on this committee.

But I want to also highlight that she was a very active committee member. Certainly, her wisdom was involved in most of the decisions that were made around the table as the committee

discussed a variety of different important subjects over the years that I've been involved with the committee, and I'm sure even before that she did just as well. So, I -- I think that the -- the key for Dr. Boyle is that she was able to synthesize the -- the discussion to the point where she could make very specific recommendations to kind of move the committee ahead or provide insights that would help the committee make important decisions, and I think that's probably the key to all that she has done for the committee over her years of tenure.

So, Colleen, I want to thank you for everything that you've done for the committee. HRSA has given -- has put together a small plaque for you that I -- I hope I can convince Carla to take back to the CDC for -- for you.

Scott, do you want to help do that? You -- you -- He -- Scott Grosse is volunteering to do that, as well.

DR. COLEEN A. BOYLE: And that's terrific. Yep.

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: All right. So, again, we -- we want to -- we appreciate everything that you've done and -- and wish you well as you rotate off the committee. You're certainly leaving the CDC representation in good hands by having Carla Cuthbert take your place at the table, but again, we want to thank you for everything that you've done for the committee. And so -- Certainly, if you'd like to say anything, we'll give you a chance to do that right now.

DR. COLEEN A. BOYLE: Well, thank you, Dr. Bocchini. I do appreciate the honor and recognition by the committee. It's -- it's really been my pleasure to serve as the CDC liaison member for -- And I think you -- I didn't realize it was quote so many years.

So, newborn screening is an area of public health that I feel tremendous passion for. In my day-to-day work here, there are not many issues that I -- I deal with that I feel like I

can have such a direct impact on people, and -- and that's just a -- it's just a really powerful opportunity.

I've learned so much during this very exciting journey in newborn screening, and I want to thank all of my colleagues that are there, many that are there today that have really shared so freely with me, and as you -- as you said, I know I leave the representation of CDC in terrific hands with Carla and Scott. So, thank you very much.

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Colleen.

(Applause)

DR. JOSEPH A. BOCCHINI, JR.: Thank you. And so, all of you know Carla Cuthbert. Carla has sat in on some of our meetings as an alternate for the CDC. She is chief of the Newborn Screening and Molecular Biology branch in CDC's National Centers for Environmental Health, and so we welcome her now as a permanent CDC representative to the committee. So, thank you.

So, next on the agenda -- Let's see, for -- for today, we're going to have a presentation on the overview of newborn screening technology, followed by workgroup updates, and then last on the agenda is two presentations related to the clinical public health implications of critical congenital heart disease newborn screening.

So, with that, let's go ahead and bring Dr. Kemper back. Alex has been working on this project for a while, reviewing the newborn screening technologies, and we're going to turn it over to him for his presentation. So, thank you, Alex.

DR. ALEX R. KEMPER: Here comes the magic clicker. So, before I get into the -- the meat of this presentation, I just want to make a few observations. So, this project came out of the recognition that newborn screening technology's kind of, at large, is -- is a fast and moving, changing world, and we wanted to put together a report just describing the very basics of this new technology to help inform the work of the

advisory committee so that everyone was, sort of, on the same page if something was out of their particular domain.

So, it gives me great pause to talk about any specific technology in front of, you know, this august group that knows much more about many of these topics than -- than I will. I mean, I'm -- you know, I feel like I'm the old country doctor in this, and I guess I'm -- I'm an expert in that -- I'm reminded of the -- the Will Rogers quote that a expert is anyone who's 50 miles away from home and has a briefcase.

So, to -- to that degree, I'm an expert in this, but -- but -- but really, I just want you to understand the spirit with which this is coming from, and it's really about just providing some basic information to help inform the advisory committee about certain technologies to the degree that they might come up in the work that we do as part of our evidence review.

So, as I mentioned before, the technologies used in newborn screening are

complex and advancing rapidly, and the advisory committee decisions depend upon understanding current technologies and anticipating future developments. And -- and, again, this work is -- was to just -- just be the -- to put together a report with the very basics of it, so that everyone understands where things are going.

So, the overarching goals of this report that -- that we've begun to work on is to describe new developments in screening methods. And when I talk about new, I'm really talking about within the past 5 years, the things that are, you know, twinkling on the horizon, so screening methods, new confirmatory methods, new treatment methods.

And what we hope to do for each of these things is put together a -- a description of -- an overview of what the thing is and -- and how it can be applied specifically to issues related to newborn screening, talk about the -- the benefits and the -- you know, the potential risks of -- you know, especially if you're talking

about treatment, and then to the degree that they might be out there, anything that we could find about costs.

So, I think of the presentation we're going to have today as -- as like the tasting menu. I'm going to, like, show you a little bit of a bunch of different things, but -- but, again, you know, I'm not a particular expert in any of these things that we're going to be talking about, and we've just begun the process of putting together the report. So, this is really to inform you of where things are going.

So, we did hold a technical expert panel for us to think about what things would be most relevant for the advisory committee, and I -- I won't read all the names, but you can see that we had experts in clinical care, in the public health laboratory side of things, and then around research and -- and regulatory issues around the technologies. So, I'll just leave this up for one more second in case you want to read it.

All right, I'll move on. So -- and this,

again, is a member of the Evidence Review Group that, you know, I would be remiss not to acknowledge them.

All right. So, in terms of looking at screening and -- and confirmatory testing, we're looking at a wide variety of things. So tandem mass spec -- Now, we're not going to go back to the tandem mass spec of the '90s and describe everything leading up to now but, really, how tandem mass spec is being used more recently over the past 5 years or what might happen with it in the future. Certainly, digital microfluidics has been a large topic of conversation. We're going to be talking about molecular tests, including, you know, what's new with PCR in targeted gene sequencing, and then next-gen sequencing.

I was doing some reading about next-gen sequencing recently. I didn't realize that next-gen sequencing is actually kind of an old term that -- that has been around for quite a while and may actually not reflect very well the new, kind of, computational things that are going on

around sequencing. But I think you get the idea that we want to do, like, you know, what -- what's current with sequencing, and then, some issues around new instrumentation, like the Genetic Screening Processor and -- and other points-of-care testing, and I'm going to be talking about some of these more in depth in a bit.

So, in terms of tandem mass spec, there's a lot of work that's gone on recently around lysosomal storage disease screening, detecting certain -- You know, it's funny. When I read, like, ceramide detection, to me, it's like saying, like, an evil humor, but the -- the ability to detect new things that may be associated with conditions that are more of interest, looking at new potential markers for a wide variety of disorders -- Pompe disease, Gaucher, adenosine deaminase deficiency -- again, thinking back to SCID, purine nucleoside phosphorylase deficiency -- again thinking back to the issues of SCID and the ways of looking X-

ALD -- Wilson disease, which, I know, hasn't been referred to us, as well as GMTN Duchenne muscular dystrophy. But, you know, there -- there's stuff going on with tandem mass spec related to these things.

And again, there -- there's approaches that might help reduce false positives, improve the assessment, or predict the degree of involvement for affected individuals. So, again, I -- I know that I'm not diving deep into the inner workings of tandem mass spec but hope to give you a flavor of the kinds of things that'll be in this report.

Again, we're looking at a wide variety of molecular tests, so DNA-based assays for screening, confirmatory testing, including PCR for first-tier SCID and SMA screening -- and as I mentioned yesterday, there -- there's great enthusiasm that the things will be able to be multi-plex -- issues of targeted gene sequencing, including, you know, more traditional sequencing for second-tier confirmatory testing, as well as

these next-gen sequencing panels that, you know, can look at a wide variety of -- you know, wide array of mutations on a -- on a panel, and then, of course, looking into the -- you know, I guess it's the present, now, as well as the near future work on whole exome or whole genome sequencing. And -- and certainly, there are a lot of projects funded by the NIH looking at this for newborn screening and for working up diagnostic dilemmas.

So, new instrumentation include digital microfluidics, the -- the lab on the chip, and we're especially interested in finding information about how digital microfluidics compares to other methods of screening that are more widely used. And I think digital microfluidics, you know, is going to be important because of the discussion around increasing point-of-care newborn screening.

The Genetic Screening Processor, which I know about this much about, allows for high throughput batch analysis of quantitative or qualitative measures of neonatal screening

samples. So, really, from what I've been able to learn so far, it can help improve the efficiency of newborn screening at the -- you know, within labs by automating more processes, and I think that there's also some work to develop other, you know, specific tests for it. And we did find a trial using Genetic Screening Processor to look at -- look for screening for Duchenne muscular dystrophy.

Again, you know, we're just in the process of working on this. So, it would give me great hesitation if anybody asked me any, like, particular question about the Genetic Screening Processor.

All right, let's talk about treatment. So, one of the things that -- that TEP recommended that -- that we look at in depth, and certainly, it's come up a lot of times at the advisory committee level, is, you know, what's going on around hematopoietic cell therapy, which as you all know is infusion of autologous or allogeneic stem cells to either allow the

production of, you know, a deficient or insufficient enzyme activity or to replace some missing cell. It can be done with umbilical cord blood, which may offer specific benefits, including things like lower risk of graft versus host disease or infection, and it does appear that umbilical cord blood is -- is more generally available, as well, so. Again, we'll define this in the report.

And then, related to this are specific gene editing technologies to fix genetic lesions, and of course, you know, I read in that great journal, USA Today, in my hotel the other day about the -- you know, the embryonic changes, so. You know, we -- we are looking for evidence wherever we can find it.

(Laughter)

DR. ALEX R. KEMPER: So, enzyme replacement therapy, again, has come up with -- a -- a lot in -- in prior reports. As you know, it can replace missing or deficient enzyme activity levels. One of the challenges with it is that

individual patients can develop antibodies which can neutralize the enzyme replacement therapy, so that can limit its effectiveness, and there's a lot of work going on to keep that from happening. Enzyme replacement therapy is also challenged in terms of crossing the blood-brain barrier, so that there are techniques that -- being put in place to address this. I mean, the -- you know, sort of, the most blunt-force one, I guess, is just the intrathecal injection, getting it directly there, to doing chemical modifications.

We're combining it with other treatments so you -- enzyme replacement therapy plus hematopoietic cell therapy. So, there's -- you know, you can -- you can put these things together.

So, relevant for, you know, SMA and -- and, I would suspect, some of the other conditions that may be nominated soon are oligonucleotide therapy. These are short, single-stranded molecules that -- that bind to mRNA and alter splicing, affecting the protein that's

developed.

So, nusinersen, which we spoke about yesterday, alters SMN2, so that you, essentially, have more of the SMN protein. This is one that's administered by intrathecal injection, but there are other therapies that are on the -- that have been developed that are similar for Duchenne muscular dystrophy and there are others in target. For example, it's interesting to me to -- to find this one that is in development to target Rett syndrome. So, this is -- this is, obviously, a very active area of investigation.

There's targeted gene therapy, so using programmable DNA nucleus to correct mutations or introduce functional gene copies. There's -- this has always struck me as kind of a funny name for anything, but a zinc-finger nuclease, which can, you know, allow for genetic editing. Certainly, the one that we hear more about in the -- in the general literature as well as the popular literature is the work that's been going on around the CRISPR-Cas9 gene editing, and -- and

certainly, there -- there's a -- a lot of work going on in a variety of conditions. I was recently in a very interesting presentation about using it to correct the mutation that leads to sickle-cell disease.

So, it's a -- it's a pretty interesting and amazing technology, and again, we're just going to have a high-level summary of this to -- to help inform the work of the advisory committee.

And then, there's all sorts of work going on around gene replacement, so using viral factors to introduce functional gene copies, and, you know, there are different viruses that are -- are being tested for doing this. I will point out that there's a Phase 1 clinical trial going on for SMA and another one for Duchenne muscular dystrophy.

Again, that's not meant to be exhaustive. I mean, there may be many other trials going on, but those were ones that we were able to find.

So, I'd like to leave it there, and

again, what -- what I hope that I accomplished in this presentation was, give you a sense of where we hope to go with this report and how we expect it to be used and the -- the kinds of technologies that we want to hit on. And so, I'm going to open this up for questions, even though I feel a little bit nervous about doing so. But I have a great group of experts working with me to put this together.

DR. JOSEPH A. BOCCHINI, JR.: Thank you, Alex. Let's open this for questions or comments to Alex. Mei?

DR. MEI WANG BAKER: Okay. Very impressive. I think even proper gene editing, I know the coding is distant.

Since you do so much, I'm going to adding on one more thing. I don't know that your group discuss about a RPC cell, the induced -- I -- I perhaps not pronounce it correctly -- induced pluripotent stem cells.

DR. ALEX R. KEMPER: Stem cells? Yeah, you know --

DR. MEI WANG BAKER: Because this is -- you use the adult samples induce, so you don't need an opinion with amniotic, because I know a lot people interesting that you -- you can combine with CRISP-Cas9 into the Cas9 to the -- have a new way to do that, even more beyond Cas9. So -- but that's the details. I thought if you keep this RP cell in your evaluation and would be good.

DR. ALEX R. KEMPER: Okay, that's a really good point, Mei. I -- I guess I should say, too -- and -- and we'll definitely add the pluripotent, you know, stem cell transformation, or whatever it's called, into here -- is that if we do this right, it -- it could be -- this -- this report could be like a living document. So, as interest in, like, some new technology comes up or whatever, it could be added in, or somebody else could, you know, go back and -- and edit what's in there as new information about that thing comes up. I'm, you know, hesitant to make an analogy to -- to Wikipedia, but -- but, you

know, that sort of living informational resource.

DR. JOSEPH A. BOCCHINI, JR.: Carol Greene?

DR. CAROL GREENE: Carol Greene, SIMD. That's terrific, and I think it will be very useful, not just for the committee but, you know, well beyond the committee, obviously.

Any thought to the technology of diagnosis? So, some of the things that are being discussed depend on having technologies like PET scanners for people who are beginning to think about, you know, can you tell when the patient with ALD is actually needing treatment? So, there's that whole area of the technology of the diagnostic testing.

DR. ALEX R. KEMPER: You know, that's really interesting. That did not come up with the -- with the TEP, because things were so much more focused on the -- sort of the genetic screening and stuff like that, but that's exactly the kind of thing that, like, over time, as, you know, those things came up, became important, that it

would be added in here. So, you know, we're happy to add in all that kind of stuff.

And -- and again, I think there's no way that we can be, you know, ever done with this document, but -- but again, our main goal is to have some sort of product, so that -- that when we, you know, are presenting topics that -- that -- that we all have, you know, sort of a common platform of understanding. And to be honest, this is going to be useful for -- for us, as well, in terms of making sure that we understand, you know, what it is that we're evaluating.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie?

MS. ANNAMARIE SAARINEN: Hi, Annamarie Saarinen, Newborn Foundation. I'm always glad that Carol finds ways to add to everyone's report so that you can have more work to do, Alex, but that's actually a really, really brilliant idea.

And I was thinking about it a little bit as you were going through, like, yeah, but the follow-up -- Because I feel like there's a lot of discussion around that at this committee is, not

just the first test that flags a child in newborn screening but the things that need to happen after that. And I will not pretend for a minute to know what all those are for the so many different conditions that still might have gaps, but I will say, having known that Dr. Kemper went through this with CCHD, it's -- it is a big deal, and it is a big deal to sort of hone in on not just better things that do the first-tier flagging the kid but what the next thing is.

And I -- I look, often, at the letter that Dr. Howell sent to Secretary Sebelius when CCHD was added and then her reply back a year later. And there's quite a lengthy section on exploring improvements in diagnostic capacity and how these things can potentially change how newborn screening for that condition is done.

But I imagine it to be true for other things, as well, so maybe there's just a -- a tack-on portion, if this a living document, that looks at those -- just a -- you know, a separate section on follow-up diagnostics, because, you

know, I -- And I think about the -- what we heard about in Barcelona at the World Congress on Pediatric Cardiology. A lot of it is based on reducing the cost and improving the ability of resource-poor places to have access to -- to echocardiograms, and we -- we did a whole poster on that with the University of Minnesota, but there were many, many presentations on this very idea, which would change a lot of how we do newborn heart screening.

DR. ALEX R. KEMPER: Yeah. Yeah. Point well taken.

DR. JOSEPH A. BOCCHINI, JR.: I have Beth on the line with a question and then John.

DR. BETH TARINI: Yes, so to piggy back, I guess, on Annamarie's comment and bring it back to a core issue in newborn screening, our core disorder is congenital hypothyroidism. So, I would like to advocate, if we as a committee decide to push through an assessment of diagnostic algorithms and what is most appropriate, I think we should take a look at one

of our oldest orders on the screening panel, which is congenital hypothyroidism.

And I've discussed this with Melissa and with Mei, that we are at a point where there are not clear standards across the United States about which children, after -- after initial screen positive, had congenital hypothyroidism that is permanent. So, I think that -- while we tend to focus on the new disorders, we still have to keep one eye to the core disorders that have been there in the (audio interference) newborn screening.

DR. JOSEPH A. BOCCHINI, JR.: All right. Beth, you were breaking up enough that I don't think everybody got a sense of your comments. Did you -- did you --

DR. BETH TARINI: Sorry. Basically, we have diagnostic challenges in congenital hypothyroidism.

DR. JOSEPH A. BOCCHINI, JR.: Okay.

DR. BETH TARINI: So, if we as a committee are going to look into this, I would

just ask that we also remember, in addition to the new technologies coming on board, we have core disorders for which it is still unclear for a significant proportion of the screen-positive population whether or not they actually have the disease and we have challenges in variation of diagnoses.

DR. JOSEPH A. BOCCHINI, JR.: Okay. Got -- Yeah, we got it. Okay. Thank you. Joan and then Dieter. (Off-mic speaking).

MS. JOAN SCOTT: Thank you, Alex, this is great, and I think this'll be a really nice document for the -- the committee. And I'm wondering if it would be helpful -- I'm looking at the list of your very excellent people as the TEP members -- but maybe to do an interview or two from folk in industry or in some of those areas that are really future looking coming down the road just to get a flavor for, maybe, some additional things that --

DR. ALEX R. KEMPER: That's a really good idea. Yeah. Well, I'll have to loop around with

you later to help gather a list of the appropriate folk to do that with.

DR. JOSEPH A. BOCCHINI, JR.: Okay, Dieter?

DR. DIETRICH MATERN: Yeah, Dieter --

DR. CATHARINE RILEY: Sorry, real -- Oh, sorry, real quick. Sorry. This is Catharine Riley. For those that are on the line, if you can mute when you're not talking, that'll help with the feedback. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Dieter.

DR. DIETRICH MATERN: Dieter Matern. Alex, so you want to write one report that includes evidence surrounding all of those --

DR. ALEX R. KEMPER: Right.

DR. DIETRICH MATERN: -- things or -- I mean, that's a lot of stuff.

DR. ALEX R. KEMPER: So, this is not -- It's a lot of stuff. You're exactly right. So, this is not a, you know, some sort of, like, systematic evidence review that's going to, like, go down into the, you know -- you know -- you

know, synthesizing all the data that are out there, but it's -- this is really like a primer that -- that's going to describe what the technologies are and how they work and, generally, what's known. So, it's like a landscape review. There's no way -- you're exactly right -- for us to do a -- a deep dive in there.

But this was really born out of the fact that -- that there -- there were some members of the advisory committee, as well as, you know, some other, you know, frequent attendees of this meeting -- just wanting to make sure that everybody understood, in general, what the technologies were. But, you know, there -- there's no way that we're going to be able to -- to, you know, synthesize everything and being on the cutting edge but just -- just have enough in there so that people understand what the issues are. Does that -- does that help?

DR. DIETRICH MATERN: Yeah, that helps a lot. The -- the reason I was asking is because

yesterday, in our Standards Subcommittee and then through my comment yesterday that apparently raised some concerns about endorsing anything -- Many of the things you are looking at are actual products, which, I assume, we're not supposed to endorse. So, how are we actually going to use such document, then, is my question.

DR. ALEX R. KEMPER: Well -- Okay. I mean -- Well, let -- let me take a swing at it, and then -- I think this is probably a better question for -- for the DFO, but it's true that most of these things are products -- right? -- but you're going to be making decisions about newborn screening that are going to use the products. You know, none of us have any conflicts related to any of these technologies, and this isn't going to be a summary saying, you know, "This is the way to go," or, "Don't use this," but just really summarize what the -- you know, what they are and what the issues are about them. So, it's not going to be, like, a Consumer Reports with, like, a red circle for, like, this

is the way to go.

DR. CATHARINE RILEY: Yeah, this is Catharine Riley, DFO. So, I -- I would agree. I think this is for information-only purposes, so I think in the context of any of the products we're discussing, if it's -- if you're sharing information or evidence or articles, things that have been published, I think all that information is very helpful, just not getting into the -- into the area of endorsing or, you know, saying, "This is one you have to use over this," I think, is where we want to be cautious.

DR. JOSEPH A. BOCCHINI, JR.: Okay. Carla? Still -- still have you, Carol.

DR. CARLA CUTHBERT: So, Alex, thank you for doing this. I think this is very helpful. At CDC, we're -- we're also thinking about a comparable kind of educational tool, as well, and I think that if we have this kind of information placed in different places, it -- it would be very beneficial for -- for people who are not actually in the laboratory.

I'm just wanting to confirm that you're -- are you planning on at least looking at all the current technologies and then everything that is maybe coming down the pike? I just want to --

DR. ALEX R. KEMPER: So --

DR. CARLA CUTHBERT: -- to confirm that because I'd like to at least make sure that we touch bases with you so that you get a good landscape, because the last thing that you want to have is someone say, "Well, I'm not mentioned. I'm not represented there."

DR. ALEX R. KEMPER: Right. Well --

DR. CARLA CUTHBERT: So, I just want to be careful about that.

DR. ALEX R. KEMPER: Right. So, that -- this issue of prioritizing things and figuring out what -- what goes in and what goes out is actually one of the -- the hardest things, because I -- there's a hundred percent chance that someone's going to be upset that we left out their technology or -- It's just going to happen. So, that -- that's where we turn to the technical

expert panel to say, like, you know, what are -- what are the good things and, you know, what things do we have to have.

I would love to be able to work with you and your CDC colleagues. Partially, I don't want to duplicate effort, and then the other thing is, I don't want to say anything that's, you know -- works at cross-purposes with what you're putting together. So, that would be great for us.

And all I can say is, in terms of, you know, whatever thing that's not in there is that over time, you know, it -- it can be added, you know. So, this is -- this document -- You know, if we do it right, it'll never really be finalized, but it'll be somewhere on a -- you know, an advisory committee or HRSA, you know, website, where it can be, you know, corrected and modified over time.

DR. CARLA CUTHBERT: I think our products are going to be different enough that there would be benefit, and it would complement each other. So, I have no --

DR. ALEX R. KEMPER: Excellent.

DR. CARLA CUTHBERT: -- no problem with that.

DR. ALEX R. KEMPER: And we can just -- Again, I just want to make sure that we don't say anything that's -- The -- the thing that makes me anxious is -- is being wrong. You know what I mean? Like, I want to be able to do a -- a fair description, and I don't want to say anything that confuses anybody.

DR. CARLA CUTHBERT: We'll do our best to have a lot of eyes over it --

DR. ALEX R. KEMPER: Excellent. That's --

DR. CARLA CUTHBERT: -- a lot -- specific eyes over it so that you get -- we get it right.

DR. JOSEPH A. BOCCHINI, JR.: Great. Carol?

DR. CAROL GREENE: So, thanks to -- to my -- Scott, to my left, pointed out to me what I missed on the slide is that the slide is screening and confirmatory testing -- I -- I think this may build on some of the other

comments -- and you've got tandem mass spec, and then, basically, DNA.

DR. ALEX R. KEMPER: Right. Well, that's --

DR. CAROL GREENE: And so, that's leaving off all the biochemical -- It's not just the imaging, which was my original comment, but enzyme assays, metabolomics, all the biochemical testing that is actually still the gold standard, not the DNA.

DR. ALEX R. KEMPER: Correct. That's -- I -- I --

DR. CAROL GREENE: And those are the labs, by the way, that are disappearing as the DNA comes on board, and we're having -- you know, we have discussions on the metabo (phonetic) listserv: Has anybody got a lab to which we can send this? Because the kid looks like he's got it, and the DNA doesn't answer the question, but the biochemical labs have gone bye-bye.

DR. ALEX R. KEMPER: Right. We actually -- It's -- it's interesting you bring this up,

because we had a very long discussion about, you know, that -- that -- that it's, really, sort of these metabolic profiles -- again, I'm probably using the wrong term, but the metabolic profiles that -- that is more associated with the disease than the -- the -- not necessarily the DNA because of the whole, you know, genotype-phenotype issues and all the things that go on modifying DNA. Boy, I know I've, like, said all that completely wrong, but I -- but I hope that I get the spirit across.

So, we don't mean to give short shrift to this, but just in the context of putting this presentation together, I just tried to put some stuff in the highlights. But we're a hundred percent with you.

DR. CAROL GREENE: Okay. And I just -- Even I missed it because it's just so much said, but if you've got a document that is for the committee and for everybody to look at that is the -- the landscape of what is the testing, and it leaves off the biochemical, then people are

not going to be working on keeping that up in pace and improvements, and it -- it just needs to be there.

DR. ALEX R. KEMPER: Right. No, I -- I -- I appreciate what you mean in terms of the -- the downstream harm that could happen if we left that out. No, but I'm -- I'm with you there, and that was my fault. I just left it off their presentation. That's why I put -- See, that's my disclaimer.

DR. JOSEPH A. BOCCHINI, JR.: Scott.

DR. SCOTT GROSSE: Scott Grosse. Also clarification: You're -- Under point-of-care screening, you're talking about new instrumentation and not existing methods, such as hearing --

DR. ALEX R. KEMPER: Well, we -- when -- what we decided -- this was very arbitrary -- just to go back, like, 5 years and then move forward, knowing that there was going to be stuff that people were going to add in to -- to bulk things up and all, but we just had to, like, come

up with some point to plant a flag in.

DR. JOSEPH A. BOCCHINI, JR.: Okay. Any questions or comments from those on the telephone?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: All right. Hearing none, thank you.

DR. ALEX R. KEMPER: Thank you very much.

DR. JOSEPH A. BOCCHINI, JR.: We do have a question from the audience. I apologize. You have to come up, and there's a microphone for you. Okay.

MS. DEBBY FREDENBERG: Hi, this is Debby Fredenberg, Texas. One of the things that we're facing as we move forward is, there seems to be some confusion between interpreting screening tests as diagnostic testing, and hopefully that -- whatever document you develop will emphasize the screening nature of it, even if it's DNA based.

DR. ALEX R. KEMPER: You know, that -- that actually makes me think that we should have,

like, a -- you know, even a section before everything goes on, disentangling what's meant by screening versus diagnosis. That's a really good point. That comes up all the time.

MS. DEBBY FREDENBERG: Right.

DR. JOSEPH A. BOCCHINI, JR.: Okay.

DR. ALEX R. KEMPER: Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Thank you and --

DR. ALEX R. KEMPER: All right, thank you.

DR. JOSEPH A. BOCCHINI, JR.: -- we look forward to your continued work and that of the expert panel. Thank you.

(Applause)

DR. JOSEPH A. BOCCHINI, JR.: Next, we -- we will hear from the chairs of the workgroups, who will summarize for us the activities of the workgroups in their individual sessions yesterday afternoon. We put this together so that we've asked the chairs to each summarize for the committee the key things within about a 10-minute

time frame to allow the committee an additional 10 minutes to discuss the -- the presentation and give feedback for the workgroups.

So, first on the agenda is Cathy Wicklund, who will present the report from the Education and Training Workgroup.

(Off-mic speaking)

MS. CATHERINE A. L. WICKLUND: I'm going to go through it all again. All right, you guys. All right. So, I think Beth's on the line, so, Beth, if you have anything to add -- Oh, you're right, Alex, this goes down, doesn't it? Yeah. Well, it's even shorter as the day goes on. So, yeah, Beth, if you have anything to add, jump in. I want to thank all of our group --

DR. BETH TARINI: Okay.

MS. CATHERINE A. L. WICKLUND: Okay. I want to thank everybody on the E&T -- or Committee or Working Group, I guess, it is now, and these are all the members, and I hope I didn't leave anybody off. So, everybody has done, like, a lot of work. We've had a couple of

projects going on that I'm going to tell you guys about and had a really, I think, a productive meeting yesterday and made some good progress on our two projects that we have going on.

So, we always kind of start with introduction of new members. We do have a couple of new members on our group and also relevant updates from members just to make sure we know what's happening in the community and making sure that we're not reinventing the wheel or doing something that somebody else is already doing.

And we then talked about the two projects that we have going on and also talked about some additional educational needs and project ideas that have come up. So, I'll go through each one of these in a little bit more detail.

The first thing that we talked about was the communication aid or guide. It used to be called the tool, so we're working on an actual name -- better name for this. And if you guys remember, this was the project that we were looking at about creating a document that

provides guidance to primary care providers on how to actually talk about the initial outer range newborn screening results with parents. The focus is more on how to discuss the results and how to communicate the results, not so much what people are -- Who's doing that?

(Off-mic speaking)

MS. CATHERINE A. L. WICKLUND: So, the document is supposed to be a -- it's not supposed to replace or have anything to do, necessarily, with the current ACT sheets and how those are being utilized, because those are very specific about the disorders and also specific about what steps the physician or the other primary care provider needs to actually take. This is really more about how you should talk to parents about it and just basically taking you back to basic communication counseling skills. So, Amy has led this endeavor, and this is the workgroup that's been working on this piece.

And what we've done, also, is, taken the resources that we had in the past -- Natasha and

Carol had done several focus groups, if you guys remember, on asking parents what's important for them to know, and so we took pieces or took -- referenced that but then also came up with a brand-new communication aid that we worked on. So, a draft was developed; it has been reviewed and revised by the small working group, and yesterday we presented it to the larger E&T Workgroup for some edits and revisions, which we're going to make and send back to the E&T Workgroup first.

Then what we want to do is get primary care providers to actually look at this and make sure that we are framing it in a way -- You know, some primary care providers, obviously, are not going to use this at all. For the people, maybe, that think about they want to use it, we want to make sure that we're presenting it in a way that is -- that they would be receptive to. And again, not stepping on toes or thinking that somebody isn't -- know how to communicate. It's framed in a way that this isn't something that you do very

often. Right? It's not often that you're getting abnormal or out-of-range newborn screening results, so, again, here are some tips to think about.

So, it's -- we're trying to get it to one page, be really short and to the point. Once we get some review from some primary care providers, we're going to bring it back to the larger committee for you guys to look at for review and comments.

And then, once that's done, we will work with ACMG for their approval and link them to the existing ACT sheets, but that won't be the only way we disseminate it. So, we'll go ahead and then, at that time, think about different ways to disseminate this.

Beth, did you want to add anything?

DR. BETH TARINI: No, I think you got it all.

MS. CATHERINE A. L. WICKLUND: All right. The second one is a project that we call the matrix or curriculum map, and we have a new name

for this, and this is a project that came out of Jeremy and Cate's group, the small working group, that is -- The -- the point of this is to be able to utilize this when you're actually creating an educational brochure. So, this is for individuals who are going to create -- okay -- going to create an educational brochure for a specific stakeholder group. It could be parents, could be midwives, nurses, physicians, and this matrix actually helps people decide on what content they actually need to include in that educational brochure.

So, if you guys remember, this was just a snapshot -- This was at the beginning; it looks very different than this -- but basically, the stakeholder and then what the content is that they would need to include in their educational brochure. So, it's really meant as a guide to help people create these materials.

There's been a lot of work on this. We changed the name, we think, to Newborn Screening Educational Planning Guide, and there's been a

lot of work done on this, adding different stakeholder groups, reviewing the content.

This was also presented at -- actually, it wasn't Baby's First Test Summit; it was Beyond the Blood -- Blood Spot -- sorry, yeah. Same thing? Okay. Good. And there were -- they invited nine different attendees to provide feedback on the actual guide itself. I think they got feedback from four, and there's also three parent workgroups that are involved in Baby's First Test that have incorporated the guide in their discussion and are also going to be providing feedback.

So, we're trying to get some of the relevant stakeholders to give us feedback on the kind of content that we have included. And we're going -- there's also a graduate student that we don't -- we're not quite sure -- When Aaron comes back in November, we'll get a little bit more information, but who's using the categories to actually look at existing educational materials and kind of see what's included and what's

already out there and use the tool in that way. So, we're going to find out a little bit more about that.

We're going to have further refinement by the working group, and then we're also going to make sure that we've asked every stakeholder to give us feedback. So, Cate's going to work on identifying which stakeholders have already given us feedback, where the gaps are, and then target those that are missing for specific review of the guide. We'll follow up with Aaron, and then once we have all that done, we'll present it to the overall committee for your review and revisions. And once that's done, we will create a list of potential partners to help with dissemination, and we're actually going to start on that right now.

The other projects that we talked about that we -- just as future projects -- One of the things that came up in our updates is basically that there are a couple of states -- Ohio and Georgia -- that have incorporated Krabbe

screening as an optional screen, and Aaron's doing some research in his state about the uptake of screening, reasons why people might decline the screening.

So, this -- well, we kind of wanted to keep an eye on this, because we think that this could be, again, a kind of a different paradigm for newborn screening, where it's not necessarily mandatory, but now it's like, here's your newborn screening panel, the pieces that are mandatory, but now you have the choice as to whether or not you really want to pursue Krabbe, or maybe there'll be other conditions that are like this as well, and thinking about that consent process and how those discussions are going.

So, we will ask Aaron to present in November to our small group, and we just want to keep this on our horizon to maybe think about presenting it to the larger group and think about what our role might be as a committee in thinking about the issues and having some of these optional tests.

And then, the second thing is coming from the cutoff in-range result discussion that we had yesterday, and there's a lot of focus on talking to -- you know, how physicians talk about or what happens with the public on abnormal newborn screening results or positive or out of range, but remember, we had a discussion yesterday about, if it's in range, and a child presents with symptoms, that just because the newborn screening test was negative does not mean we can completely eliminate or rule out one of those conditions, and they need to be worked up appropriately. So, again, how can we, maybe, educate providers or public on, really, what a normal or in-range newborn screen result actually means.

So, Amy reported yesterday that her and Sue Berry -- and, Sue, you're here if you want to add anything -- are working on a project regarding normal end-range newborn screening results, and this is more -- seem to be more focused on the parents and the public and

understanding. We're going to keep an eye on what they're doing and then see if there are some gaps that we can maybe fill in or just think about how we can help them in their process of moving forward.

So, I think that's it. Does anybody have any questions? Or, Beth, did you want to add anything?

DR. BETH TARINI: No, I think we should stick with the questions.

DR. JOSEPH A. BOCCHINI, JR.: All right. Thank you, Cathy. So, this is open for questions. So, Mei?

Dr. MEI WANG BAKER: Yeah. I -- I like the idea in terms of put some effort into education primary care physicians. That's what we're dealing with all the time. Did you think about get AAP involved with that?

MS. CATHERINE A. L. WICKLUND: Yes. So, once we get all of this done, then, you know, we are going to kind of think about, like, the connections we have on our committee and leverage

our own professional organizations to be able to think about dissemination in a broader way.

DR. JOSEPH A. BOCCHINI, JR.: Melissa?

DR. MELISSA PARISI: And sort of -- Melissa Parisi, NICHD. So, as follow-on to that, I was just going to mention the Intersociety Coordinating Committee, which is a body convened by NHGRI and other groups, who you're aware with, of this group that might actually be a good venue for some of the provider-focused educational efforts around newborn screening. They also have an interactive website that has a number of training modules available, so there might be an opportunity to put some of your materials on the G2C2 site.

MS. CATHERINE A. L. WICKLUND: That's a great reminder. I knew about them and had not thought about them. So, thank you.

DR. JOSEPH A. BOCCHINI, JR.: Let me just let Bob do the follow-up with that. Go ahead, and then --

DR. ROBERT OSTRANDER: Yeah, I just

wanted to mention that I'm -- I'm also the AAFP rep to the ISCC, newly, so I mean --

(Off-mic speaking)

DR. ROBERT OSTRANDER: -- I'd be happy to serve as one of those bridges, and we actually had our call just before I missed my flight down here, and I pointed out that we have these organizations of organizations that are somewhat siloed from each other and doing similar work. I mean, they're doing genetics/genomics across the board, but that we -- even our organizations of organizations shouldn't be so siloed, so --

MS. CATHERINE A. L. WICKLUND: Thanks. I appreciate that.

DR. ROBERT OSTRANDER: -- feel free to use me as part of your --

MS. CATHERINE A. L. WICKLUND: We'll be reaching out, yeah.

DR. ROBERT OSTRANDER: -- part of your bridge.

MS. CATHERINE A. L. WICKLUND: Yep.

DR. JOSEPH A. BOCCHINI, JR.: Jeff?

DR. JEFFREY P. BROSCO: Jeff Brosco. I noticed that you used the term for -- communication aid for primary care doctors as opposed to an info sheet. Why do you say communication aid?

MS. CATHERINE A. L. WICKLUND: Because it's not really an information sheet in the sense of information about what newborn screening is. It's not a fact sheet as much as a, remember these tips when you're talking to parents. So, it's an actual, like -- It's more about the communication process as opposed to information about newborn screening. I'm not sure if --

DR. JEFFREY P. BROSCO: So, you know --

MS. CATHERINE A. L. WICKLUND: I'm -- answering your question.

DR. JEFFREY P. BROSCO: -- it does, and that's what I thought. I mean, because I've been -- I teach -- part of my teaching effort is with communication skills, and there's a whole science behind --

MS. CATHERINE A. L. WICKLUND: There is.

DR. JEFFREY P. BROSCO: -- the actual words that you choose, and I've found that a lot of this is actually modeling the kinds of ways that you say things. So, I wonder if that's what you're talking about, that you have communication science experts on your team who are thinking about how, exactly, to word stuff.

MS. CATHERINE A. L. WICKLUND: So, one of the things we did talk about was -- So, first of all, we have -- I mean -- So. We -- one of the things we talked about was whether or not we wanted to put this out to somebody who is, like, more of an expert in health communication. So, we have genetic counselors involved, who a lot of what we do is communicate.

But you're right, it's not necessarily the same as the entire communication science behind it. So, we're kind of drawing from some of the counseling literature that we utilize and some of the communication piece. But I think that that's a great suggestion.

DR. JEFFREY P. BROSCO: Yeah. And I -- I

would be careful, too, because when you -- Sometimes you say communication science; then you start thinking of people who are major in communications and think about public stuff. And this is more, probably, in the realm of psychologists and that kind of research, and how one-on-one, when you're talking to people --

MS. CATHERINE A. L. WICKLUND: Yeah.

DR. JEFFREY P. BROSCO: -- that the words you choose have important meaning.

MS. CATHERINE A. L. WICKLUND: Yeah. And again, genetic counseling really draws upon that literature extensively in the training, so that is there, but then there still is the health communication piece that's not so much broad messaging but still, you know, focusing, again, on one on one, as well. So, I feel like we certainly have the genetic counseling piece side of things covered, but I still think we could benefit from somebody, maybe, who's looking more specifically at that process.

DR. BETH TARINI: This is Beth. Excellent

suggestion, Jeff. Do you have any people you'd recommend we reach out to?

MS. CATHERINE A. L. WICKLUND: I actually have somebody, Beth, in mind, so -- But, Jeff, if you do --

DR. BETH TARINI: Okay, never mind.

MS. CATHERINE A. L. WICKLUND: -- I'm happy to, but I have someone down the hall that I work with, too. Yeah.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie.

MS. ANNAMARIE SAARINEN: Yeah, building on Jeff's suggestion -- There is a lot of new stuff, just in the last 2 years, that's been done on communicating with families around vaccines, just because of all the drama, and it's -- it's truly, like, front-line pediatrician kind of stuff, and I think that would be a great place to look at resources, too.

MS. CATHERINE A. L. WICKLUND: Yeah. And -- Amy, are you on right now?

DR. BETH TARINI: She is not.

MS. CATHERINE A. L. WICKLUND: She's not,

okay. Because I know that she did, when she put this together, utilized a lot of different resources, and when, you know, she went -- It -- it wasn't like something that she just kind of came up with. She definitely utilized some literature and brought it into it.

MS. ANNAMARIE SAARINEN: Well, and maybe to his point -- and -- since you don't have the slide up anymore, but if it just said communication sheet -- and he was asking about what's the difference between an info sheet versus a communication sheet, but if -- if -- I -- I totally get your intent, but maybe if it's still called communication sheet as the big headline, maybe there's a sub-headline underneath that that says: communicating newborn screening to parents. Like do something --

MS. CATHERINE A. L. WICKLUND: We would love some great --

MS. ANNAMARIE SAARINEN: -- so they absolutely know --

MS. CATHERINE A. L. WICKLUND: Yes. You

guys have good ideas for the title. Like, we have not landed on any title to this at all, so if you have some suggestions, we'd love to hear more.

DR. JOSEPH A. BOCCHINI, JR.: Carol?

DR. CAROL GREENE: Relating to that question, and I haven't seen it recently, but maybe taking a step back -- and I'm not sure what the focus is at this point -- but a step back to the focus group that Natasha and I did, and there may be some elements about, you know, what words to use in communicating, but this was, at least originally, more along the lines of, you know, "Nobody told me how --" People want to know, how many days before I get the result, how worried should I be.

It's not what words do you use, but is it high, low, or medium, people saying they didn't get told whether they had to stay up at night and watch their child, whether they had to go immediately -- were they going to have to go to a hospital. They were just told, but -- And -- and also basic things like, ask the family, do they

want a lot of information, or do they want to just wait for the results to learn about the disease.

So, this was not really -- I -- I mean, I don't know what it looks like now, but it's more along the lines of, what kinds of things do -- have families told -- have families said that they want to know, so that the pediatrician, instead of just talking about PKU, might take a step back and say, "Do you want to know about the disease, or do you want to just know about the process to find out if your kid even has it?" So, it was, really, more high level.

DR. JOSEPH A. BOCCHINI, JR.: Jeff.

DR. JEFFREY P. BROSCO: Just a follow-up and I like -- just hear how you said that: Do you want to know about this or that? I lot of physicians say something like -- Some families in this position want to know everything; they want a lot of information. Other families would rather just know the big ideas: How -- what kind of family are you? I mean, what do you really want?

And phrasing it that way gives people permission to choose either way.

So, I think that you're absolutely right that it's both. It's not just the PKU science; it's, what do you want to know, but even how you word that. And you're -- you know you're going to ask: What's going to happen in the future? What's he going to be like? Is he going to go to -- go to college? And so, how you talk about that makes a huge difference, because if the first thing you say is, "I don't know," then that gives people a pretty scary, negative message.

DR. JOSEPH A. BOCCHINI, JR.: Go ahead, Annamarie.

MS. ANNAMARIE SAARINEN: Sorry, this is Annamarie Saarinen again. Didn't Genetic Alliance and Baby's First Tests do a ton of this parent communication stuff, like, 7 years ago? Like, there -- I remember an ad agency, like, being at some of these meetings, and there was some -- and Carla, were -- you were -- did some sub-workgroup presentations on this kind of thing, too, on

communicating, correct?

DR. CARLA CUTHBERT: That had to do with the -- I think the 50 years of newborn screening. We'd gotten -- put some communication materials together, and that was -- I know that APHL took the lead in -- in some of those activities. You know, we can, again, get in touch with you guys and have APHL communicate with -- with you about that.

MS. NATASHA BONHOMME: So, I guess I would say there have been a lot of activities that have taken place --

FEMALE SPEAKER: Natasha, can you state your name, please?

MS. NATASHA BONHOMME: Oh, sorry. I thank you for the reminder. Natasha Bonhomme, Genetic Alliance. I think there have been a lot of different activities that have taken place around different topics. So, there was one, like Carla was saying, about the 50th anniversary and thinking about messages around there. There's the work that Genetic Alliance did with Carol that

was just speaking about -- around a very particular topic on consumer-focused newborn screening. There are messaging platforms that Genetic Alliance has done through Baby's First Test to reach out both to parents and health providers and others.

So, I think there are a lot of different things happening but not necessarily a -- You know, at the end of the day, we -- I would say, as a community, we still haven't narrowed down on what is our one key message about newborn screening.

So, I think there are a lot of different things that are building upon each other. I think the work that's happening in the workgroup, I think, builds off of and references the work that we did a number of years ago with those focus groups, but it's not meant to replace or to be, like, the 2.0 version. It's really just relating back to it and taking some of those lessons learned. But I agree, there have been a lot of different pieces that have happened, for

different reasons, over a bunch of different periods of time, but not necessarily a whole mapped-out plan around that.

MS. CATHERINE A. L. WICKLUND: I think that's why we struggled with this project a little bit, too, was to think about, really, what the purpose of it is, and so it took a while to kind of -- like, knowing all of the things that have happened, taking in -- that into account when we did this. It kind of -- We didn't do anything with it for a long time except for kind of talk about it a lot, because we knew these things were happening. And then, kind of knowing all of this stuff that's happening, trying to hone in on what we really were trying to actually convey, finally, then, helped us kind of move it forward. Good?

DR. JOSEPH A. BOCCHINI, JR.: Okay. Any questions from those on the telephone before we move on?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: If not,

Cathy, thank you, and thank you for the work that the workgroup is doing. Thank you for your leadership.

All right, next, Jeff Brosco is going to give the update from the Follow-Up and Treatment Workgroup.

DR. JEFFREY P. BROSCO: Good morning, everyone. So, we, as you know, have two sub-workgroups, and both of them are really concluding their work, pretty much. So, the Medical Foods for Inborn Errors of Metabolism -- the report was affirmed at the last Secretary's Advisory Committee, and it's really in the final stages of editing, and we think that it should be complete -- complete, complete by the next meeting, and thinking about publication, some folks think we should go -- go big and go for policy, maybe in JAMA or something like that, but we have a variety of other places we think we can submit.

We talked at length yesterday about the quality measures for long-term follow-up and --

that Alan has -- has led over the last 15 months, and we also talked about, yesterday, how we think that the final report, at least a -- a pretty good draft should be done for the November meeting, and we talked a little bit about, yesterday, how we want to frame this final report. And we think the way to do that is to say that this is sort of the -- the next step in an ongoing series of actions that the Secretary's Advisory Committee has taken to improve long-term outcomes for children with newborn screening conditions. And we think this would be, really, the bulk of the work that we do for the next few months leading up to that meeting.

I know you see these every time. I just want to keep reminding folks that there are -- there was a tradition of what we've been working on, and so we're going to continue to follow this pattern of the papers that have been done before, and we're still using this framework for assessing outcomes from newborn screening. This is the -- sort of our roadmap for what to do

next. And of course, what we've done with quality measures is look at this final, right-hand column of measuring concepts, and that's what we worked on and presented yesterday.

So, here's the summary from yesterday. I'm not going to go through it again, but the big idea is that quality measures are a crucial part of what we do, many different types of quality measures, and collecting these and creating these can be very challenging, and that, lastly, the -- the patient/family/consumer perspective is essential.

So, what happened yesterday? Well, we had 120 minutes of wide-ranging, passionate, no-holds-barred discussion. It was great. The -- I -- I -- it's hard to convey how much energy was in that room, and it was really wonderful to see that even as we're getting past 5:00 and they're closing the building down, people still wanted to talk about this. So, it's clear there's a lot here.

So, a couple, sort of, take-home points

from this: One, I think, is that we recognize that quality measures are really a tool -- right? -- or maybe a toolkit, for all the things we want to do for improving long-term outcome and aren't really an end in and of themselves. So, that's why we want to, sort of, wrap up the work of the Quality Measures Workgroup and think about what our next steps are.

So, this is really a time to step back and think, what are those next steps. The good news is, Alex and K.K., as -- You sort of -- Alex just did a -- sort of an update on -- on what the diagnostic and confirmatory testing are. Well, he and K.K. and their team are also going to be doing, sort of, a scan of current long-term follow-up activities across the U.S. And they're planning to present at least an -- an interim report at the November meeting, so that would be a good chance for us to hear, what are some of the things out there and how we can help.

We also learned yesterday about a couple of other sorts of efforts in this area that we

think we can have presented, either maybe on a call between now and November or at the workgroup meeting in November. So, that'll help us think about concrete next steps.

And then, it -- it turns out -- It's a funny thing. When you're trying to reach consensus with 25 people at the end of the day, it can be really hard, but when you are alone in your hotel room at 5:00 a.m., it's very easy to reach consensus. There's just -- No one disagrees with you.

(Laughter)

DR. JEFFREY P. BROSCO: And so, I came up with a strategy for trying to organize our efforts as we move forward, and people can disagree afterwards, but at least for now, we have consensus.

(Laughter)

DR. JEFFREY P. BROSCO: So, one of the ways to think about is -- is that children with newborn screening conditions fit into basically four different populations or groups and that

each of these four populations offers the opportunity for measuring and improving outcomes. That is -- And there are a lot of activities already happening. And one of the, sort of, founding things is that we need to make sure the child and family perspective are included in all these populations. I think that one of the nice benefits about our workgroup is that we really do have the range of stakeholders represented, so we can do a good job of making sure that all those activities fit.

So, what are these four populations? So, this is one way to -- to look at it, and you can start by saying that any child with a newborn screening condition, say sickle-cell disease or cystic fibrosis, they are part of that group. They belong to a group of children that have that condition or related conditions.

At the same time, they're also part of the group of children that's been identified as having a newborn screening condition. So, they fit into that slightly larger group.

And then, because of their medical condition, they also fit into this larger group of children with special health care needs. So, they fit there.

And lastly, of course, they fit into the group of all children.

And if you look at these four groups or populations or levels -- I'm not sure what the right way to -- to say it is -- you can see that there are quality improvement, long-term follow-up monitoring activities that happen for each of these levels. And so, that's one of the ways, I think, we might organize our steps forward.

So, again, if we start with specific conditions -- sickle-cell, MCAD, whatever it may be -- here's the area where we see a lot of the, sort of, formal quality measures being developed -- you know, is this child getting penicillin; has he received, you know, a transcranial Doppler. I mean, those sorts of things happen. The measures are being developed, there are formal QI activities around it, there are

research networks built up around particular specific conditions, and there are ways we might be able to nudge these forward.

There's a lot of different ideas about we could improve the electronic medical record. Some of the ideas were these, sort of, plug-ins that Alan mentioned yesterday. Cathy and others mentioned the idea of just using a dot phrase. And so, there are ways that we can help move the electronic medical record forward in specific conditions.

There was probably the most interest yesterday at our workgroup about how we can tap into family/patient advocacy groups as a real critical driver. So, if we have a web-based thing, if we have an app -- and I think this is something you mentioned yesterday, too, Dieter, that this may be one of the ways that we can cut across a lot of the systems that don't seem to talk to each other. And NORD is doing this, there's Newborn Screening Connect, and there are probably a lot of others. So, I think this is

going to be one of the things that our workgroup is likely to, sort of, jump into once we have a better sense of who's doing what.

So, that first group is pretty straightforward. Those are children who have a specific condition.

And then, there's a group of children who have any condition identified by newborn screening. Most of the monitoring and quality improvement stuff happens while it's at the state level, and -- whether it's the lab or Title V or some other state-level group. But they want to know how well the system is working. And NewSTEPs is, sort of, the early part of that, but what comes after it has been a big question.

And the good news that we learned is that there's a fairly large collaborative effort that had started among a bunch of states and includes NewSTEPs, includes the LPDR -- that's the Longitudinal Pediatric Data Resource -- and the National Coordinating Center, and so we think that this is -- we want to learn a lot more about

what this group is doing and see what it is that our committee, that our -- the Secretary's Advisory Committee may do to help move that forward. Because that's obviously right in our wheelhouse.

At the level of children with special health care needs, we talked about how there is this National Survey of Children's Health that's -- it's done through HRSA and now includes children with special health care needs. And so, one of the ideas is, if there is a way to identify which of the children in this broad-scale, population-level research or data has a newborn screening question, that would begin to help us understand, at the state level, at least, and maybe at some Census tract level, what's happening with children who have a newborn screening condition.

And then, lastly, are -- are all children, and I -- I mentioned yesterday that so much of what's happening in value-based reimbursement, what's driving health care

nowadays, is looking at all children. It's not really looking at children with special health care needs or newborn screening conditions. That smaller population tends to get lost. So, promoting the use of outcomes that are relevant to children with special health care needs might be something that we can think about as a group.

And to sort of come back to that idea, I -- I redrew these four levels, or four populations, of all children and children with special health care needs. So, there are about 80 million children in the United States, and maybe about 15 million or so have a special health care need. And that, kind of, red dot that you can't write anything in, that's probably less than a million children that have a newborn screening condition. And I think it's important, sometimes, to see what a small number of children it is that we're dealing with.

And so, my key points from this, I think, are that child health policy really should reflect the needs of children with special health

care needs, including those with newborn screening conditions, and it behooves us to try to pair up with those 15 million children because, otherwise, it's easy to get lost when health policy's made. Right now, it seems like most health policy's about all children.

On the other hand, you can sort of flip that around and say that children with special health care needs and -- and those with newborn screening conditions are more vulnerable to the factors that affect everyday health of children. So, whether it's poverty, immediate environment, school, family issues, our kids are particularly vulnerable to those sort of environmental and -- and larger issues. So, this means that for improving the health of children and outcomes of children with a newborn screening condition, it behooves us, again, to think about policy for all children.

And with that, I will stop and see whether people agree at all.

DR. JOSEPH A. BOCCHINI, JR.: Thank you

very much. That was very -- very nicely organized. Great.

Questions, comments? Melissa.

DR. MELISSA PARISI: Melissa Parisi, NIH. Jeff, I -- I like this strategy for trying to contextualize the specific conditions and developing approaches for an individual population of those with newborn screening conditions and then putting it into the context of all children.

In -- in fact, this is a little bit off topic, but yesterday, on my drive home, I was listening to NPR, and they were talking about the strategy that LBJ used to try to push Medicare through and really trying to say, "Look, you know, do you want to be a part of something that's going to improve health care for, you know -- for people as they get older, and in particular so you can tell your grandchildren, 'I was part of that legislation.'" So, I mean, it -- it's a little bit of a -- of a twisted analogy, but I think, when you talk about policy, I think

putting it into the larger context actually does make a lot of sense.

And I think one of the things that we were struggling with yesterday during the discussion about quality measures was whether to be focusing on individual rare newborn screening conditions versus thinking about them as a larger group, and I think if you think about it in these different levels or buckets or however you want to, you know, stratify it, that actually gives us a way of moving forward in these four different domains, you know, because I think there are quality measures that might apply in those individual subgroups, but then there are ones that also would apply for -- for the children with special health care needs and potentially even reflect improvements in health care for all children.

So, I guess, you know, maybe I've drunk the Kool-Aid rather quickly, but I do actually like this way of thinking about it.

(Laughter)

DR. JEFFREY P. BROSCO: All right, we've got a consensus of two now.

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: Other questions or comments? Carol Greene.

DR. CAROL GREENE: Consensus of three. Carol Greene, SIMD. This is, I think, something that just beautifully and visually captures some of the things that I was interested in when I was -- when some of us were saying, try and capture things that are not necessarily disease specific because of the problems to get it in. And this is just a beautiful, concise representation of something that, I think, will have a lot of value.

DR. JEFFREY P. BROSCO: Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Other questions, comments? How about on the telephone?

(No audible response)

DR. JEFFREY P. BROSCO: Okay, this is not what our meeting was like yesterday.

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: Well, Jeff, I think that this was a very nice way to --

DR. CHRIS KUS: This is Chris Kus. I've got a comment.

DR. JOSEPH A. BOCCHINI, JR.: Yes, is there someone on the phone?

DR. CHRIS KUS: Yeah, this is Chris Kus and --

DR. JOSEPH A. BOCCHINI, JR.: Go ahead, Chris.

DR. CHRIS KUS: -- I have a comment. Just to make -- I -- I don't know about the other people at our meeting, but during the meeting yesterday, people would be talking about the Maternal and Child Health Program and the Children with Special Health Care Needs program as separate programs, while Children with Special Health Care Needs is part of the MCH population and gets -- is supposed to have 30% of the Title V dollars.

DR. JEFFREY P. BROSCO: Yes. True.

DR. JOSEPH A. BOCCHINI, JR.: Okay. Thank

you. All right.

Well, thank you and the committee and the workgroup. I think moving this along quite well, and I like the formulation. Thank you.

DR. JEFFREY P. BROSCO: Thank you. All right -- Annamarie.

MS. ANNAMARIE SAARINEN: I'm sorry, Mr. Chairman, but I was trying to add the November meeting invite to my iPhone calendar, and I think it inadvertently sent the meeting invitation for November to everyone on the committee. So, apologies. I am, like, taking Catharine's job for, like, 2 seconds today, but I didn't want you to all freak out that you got this weird email from me.

(Laughter)

DR. CATHARINE RILEY: Thank you. If everyone can just add that -- This is Catharine Riley. If everyone could just add that to their calendar.

DR. JOSEPH A. BOCCHINI, JR.: Consider it done. Okay. All right.

So, at this point, we're going to take a -- a short break, from now 'til 11:30. We'll all be back here at 11:30 for the final portion of our second day of the meeting. Thank you.

(Whereupon, the above-entitled matter went off the record and then came back on.)

DR. JOSEPH A. BOCCHINI, JR.: Okay, we're ready to restart the meeting to -- If everyone can take their seat, we're ready to start.

So, we do need to take another roll call before we start this session. So, on the telephone, Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Mei Baker?

DR. MEI WANG BAKER: Here.

DR. JOSEPH A. BOCCHINI, JR.: I'm here. Jeff Brosco?

DR. JEFFREY P. BROSCO: Here.

DR. JOSEPH A. BOCCHINI, JR.: Let's see, Carla's not back yet. Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH A. BOCCHINI, JR.: Joan Scott?

MS. JOAN SCOTT: Here.

DR. JOSEPH A. BOCCHINI, JR.: Fred Lorey?

DR. FRED LOREY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Dieter Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Beth Tarini?

DR. BETH TARINI: Here.

DR. JOSEPH A. BOCCHINI, JR.: Cathy Wicklund?

DR. CATHERINE A. L. WICKLUND: Here.

DR. JOSEPH A. BOCCHINI, JR.: And Catharine Riley?

DR. CATHARINE RILEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: For the org

reps -- Dr. Ostrander is on his way. Michael Watson?

DR. MIKE WATSON: Here.

DR. JOSEPH A. BOCCHINI, JR.: Britton Rink?

DR. BRITTON RINK: Here.

DR. JOSEPH A. BOCCHINI, JR.: Kate Tullis?

DR. KATE TULLIS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH A. BOCCHINI, JR.: Chris Kus?

DR. CHRIS KUS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Adam Kanis?

DR. ADAM KANIS: Here.

DR. JOSEPH A. BOCCHINI, JR.: Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH A. BOCCHINI, JR.: Siobhan Doyle?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH A. BOCCHINI, JR.: Cate Walsh Vockley?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: And Carol Greene?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: So, as we resume, we have a presentation by Kellie Kelm and -- who is chair of the Laboratory Standards and Procedures Workgroup, who will give us that update.

DR. KELLIE KELM: Thank you very much. So, last but not least, our workgroup -- And so, we had a great discussion yesterday, and our main time that we had set aside was to discuss the draft of the best practices for state newborn screening labs and programs on cutoffs, discussion around that, and then we had actually set aside a brief time to discuss some new topics, but I think we took another hour on that, so we had a lot of great ideas during that brainstorming session to share.

And so, here's our current workgroup roster, and I want to thank everyone. Pretty much everyone made it, and we had some additional people joining us, so it was a -- a great group.

So, this is just a reminder of our workgroup charge, and most of the time, the two projects that we had assigned to us were focused around number 2 and 3: lab procedures utilized for effective and efficient testing of the conditions included in the newborn -- in the Uniform Panel, infrastructure and services needed for effective and efficient screening of the conditions included in the Uniform Panel. And that included, sort of, reviewing timeliness data around the recommendations that we made to the committee and the committee accepted a few years ago, which we're hoping to get a snapshot of, maybe, by the next meeting, as well as evaluating new -- next-generation sequencing and the role that that plays in newborn screening now and going forward.

But we were asked by Dr. Bocchini and the

committee to consider the draft that had been put together by APHL's QA/QC Subcommittee, and -- as they're writing this paper that's going to be a guideline for determining cutoffs, after a lot of the discussion that we've had, as well as, you know, based on the media reporting.

So, the presenters are the chairs of the -- this -- writing this guideline, and that is Dr. Rocini and Patricia Hunt, and they participated by -- by phone to present a brief draft, which is really what I'm going to show you, which was a couple of slides with some bullets that we had.

So, this is this draft -- draft guidance document on how to determine cutoffs, so, you know, there's some discussion about whether or not this is a -- a guidance or whether or not this is a best practice document, and I think we had a lot of discussion about that. And so far, a subset of the subcommittee has contributed, others now reviewing, and then following is this draft outline.

So, this is the membership of the QA/QC Subcommittee, and you can see that it has quite a broad list of participants. And Dr. Rocini also asked that I point out Amy -- I hope I say this right -- Hietala, from Minnesota, who's really been helping a lot in terms of -- with this draft.

So, the purpose of the document is to provide an overview. You know, the idea is to have -- to be able to point people to resources of some of the approaches that newborn screening programs may take in determining a cutoff between abnormal and normal screening test results. This is not meant to cover all possible methods of determining if a sample is screen positive. There are other resources available, but the idea is to have a good starting point for labs that have resources available.

So, very briefly, you know that the draft will include just a discussion of what a cutoff is. Obviously, it can either be at the low end or the high end depending on, you know, what you are

trying to identify and, obviously, the nature of the -- the test, the biomarker, and sometimes you're looking for, you know, high or low. And so, usually, this is done by, 1) performing a small population study, 2) evaluating demographic factors that may impact a reference range, and 3) determining the normal reference range of the population graphically, and -- and here are a few ways that you can do that.

So, after you determine the normal reference range of the population -- your population statistically, conduct your literature search, or use other information to identify prevalence and incidence of the disorder, and any published reference ranges or cutoffs -- and we did talk a little bit about how this can be difficult for newer conditions that are added to the RUSP, for example -- contact other states that are running the test, ask for their cutoffs for comparison, and evaluate the results of the population study compared to two positives.

So, there are other -- you know, so

cutoffs for specific newborn screening disorder categories; there are considerations for some of these things that are listed. Challenging the preliminary cutoff -- So, you'd run known positive -- positive from other states or positive for positive controls using PT specimens, if available, in comparison, once again, to other programs, and obviously, you have to take into account special considerations, the simple ones -- age/birthweight dependencies -- but then, obviously, for the first lab to set up screening, that makes it, also, very difficult. And then, what are some possible guidelines for monitoring and evaluating the cutoff and -- and offering references as part of the guideline.

So, just to go back really quickly -- So, some of the interesting discussion that we had after we reviewed -- they reviewed this very brief outline, if you will -- Some of the suggestions that the committee had and some of the feedback that we heard -- You know, the questions were: Will analytical tools, such as

R4S and CLIR, be included in the guideline? And the answer is, it will be. The document should recommend to programs that they -- that they take this and then have their own SOP and that the SOP is written and available, and that recommendation should be made that they have a documentation and the authors -- the -- the chairs said that that was good feedback.

One of the things that even came up yesterday is people understanding -- including best practices or guidelines for how labs evaluate when a signal, for example, a false -- a negative shows up and how -- Because they talk about monitoring and evaluating the cutoff here, and obviously, there's periodic monitoring and evaluation, but, you know, obviously, you know, when you have a false negative that comes to your attention, if the evaluation is different, including that description in that section. So, similar to what Alex said about his technical review, the chairs said they intend that this document is a living document that can be defined

over time, and so that was one other thing, is that this is not going to be one set in stone.

And so, they gave us a brief overview of what they thought of in terms of their timeline. So, they are -- the subcommittee is writing and reviewing. They're going to incorporate some of the feedback that we gave them yesterday, and then they'll be moving the draft on to their APHL Newborn Screening and Genetics and Public Health Committee in October, with the plans to actually present it here in November to the committee in order to get our input.

And -- and we actually brought that up, our workgroup, as very important in order to get committee input and whether or not there was going to be a way for us to do that. So, when they come in November, the intention is that it would be draft, and there would be opportunity for the committee to weigh in on -- on -- after we have a chance to read the draft. So.

So, moving on to new topics -- And a lot of these, we felt, lay within our existing

workgroup mandate already, and they're presentations that I think will be very interesting. They weren't, necessarily, anything that was a project for our committee but just sort of some topics that we discussed that we'd like to hear about in -- in the future.

So, Mike Watson brought up that, pretty soon, there was going to be completion on two projects: looking at detection of hearing loss using a -- what we consider, I guess, molecular first-line screening test. And so, this is -- the intent of this was to pick up the late onset hearing loss cases that are not detected by the current hearing screen. And so, these are usually later onset, between birth and school age.

And so, we had an interesting discussion about whether or not when you have -- You know, this is, obviously, as we said, unlike the first-line test, and it's picking up different conditions within hearing loss, but, you know, is this considered a -- an extension of the current condition on the RUSP because hearing loss is

already on there, or whether or not this would be different. And I believe there was some discussion, because CMV, for example, was part of this, and -- and whether or not CMV comes and -- and how we'd handle that if it wound up being nominated separately, so.

The second thing we thought would be interesting was to get an update on the NSIGHT projects, but specifically the projects -- or the part of these projects where they were comparing next-gen sequencing to traditional newborn screening. We know that some of the grantees had that as a specific part of their projects that they were doing. And some of the data had already been published or presented at some meetings recently.

There was also a discussion about whether or not there was -- whether the -- the workgroup wanted to consider or discuss other possibilities for national data aggregation of newborn screening data outside of R4S and CLIR and NBSTRN. Obviously, you know, newborn screening

data is big data. It's out there; it's, you know, something that could be used. And we, of course, discussed a lot of the problems that people have already experienced trying to do CLIR and NBSTRN and other kinds of big data projects. And so, I think -- we didn't get into it much, but it was brought up as something to think about.

Although we've had some presentations in our group about second-tier testing, there was a specific request for us to focus on second-tier testing for the new conditions that were recently added to the RUSP, and so discussing both some of the molecular, sequencing-type second-tier testing as whether -- as -- as also the mass spec-based second-tier testing for things like MPS1 and et cetera.

And one of the things that was brought up to talk about was a NewSTEPs peer network and sharing that information and how that's being used, and also just a presentation, perhaps, from New York on their next-generation sequencing panel that they're using for SCID second-tier

testing and the work that they're doing with CDC on that in some of the -- Because I believe they're funded and -- with some items that they're giving to CDC in return. So, that -- that would be really interesting to hear about that -- that project.

And last, Amy Brower suggested a report on the NICHD pilot studies for LSDs that NICHD had funded, and those are ongoing.

So, I believe that is all that I have, and anyway. So, we have lots to -- lots of presentations and -- and meeting ideas that we had for the future. So, any questions, comments?

DR. JOSEPH A. BOCCHINI, JR.: So, thank you very much. This is really a nice summary of what you've done and what you're looking at going forward.

Are there questions or comments at this point? Melissa?

DR. MELISSA PARISI: Melissa Parisi, NICHD. So, since several of your new topics involve some of the NICHD-related projects, I

thought I would just make a comment.

And you're absolutely right; with -- with regard to the NSIGHT projects, one of the groups at UCSF is actually looking at a comparison of next-generation sequencing versus conventional newborn screening, and their preliminary results that, I think, were presented at ASHG last year showed that about 75% of the conditions were being picked up by next-generation sequencing, which was considerably less than people might have predicted on the basis of a comprehensive type of whole exome sequencing approach. And they're actually exploring reasons why this might be the case, and I think it's actually been very informative. And -- and, you know, kind of why we're doing these pilots in the first place is to really try to learn what the issues are.

So, I would hope that, you know, within a year or so, they would have more complete data sets and be able to follow up and give us some really informative information about that pilot and -- and the findings from that study.

So, I certainly endorse that and also agree with some of the pilot studies for the LSDs. There have been some delays in getting some of the states' pilots off the ground, but I think, again, within a year or so, we'd have some really nice data to present, as well, from some of those pilots, particularly for Pompe, MPS1, and -- well, for those two in particular. So, thanks.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. Other questions, comments?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Questions from those on the line?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Okay. Kellie, thank you very much. Appreciate the work that you guys are doing in that committee workgroup.

All right, next on the agenda, we have two presentations related to critical congenital heart defects. The first presentation will be Dr.

Scott -- by Dr. Scott Grosse. Dr. Grosse is a research economist at the National Center on Birth Defects and Developmental Disabilities, the Centers for Disease Control and Prevention. He serves as the federal advisor to the Evidence Review Group that reviewed proposed -- that reviews proposed conditions for the advisory committee. He will focus on the public health implication of critical congenital heart defect screening.

So, Scott? Thank you.

DR. SCOTT GROSSE: Thank you. Today I'm going to be talking about the specific effect of state newborn screening policies on infant deaths from critical congenital heart disease. That's only one measure of outcome, but it's one that's objective and that can be measured using existing data sources. We're not evaluating the effect of hospital-level screening. We're looking at, what is the effect of a state policy that calls on hospitals to do the screening. That's a critical distinction.

I think most people have -- here are -- have some familiarity with critical congenital heart disease. It has been operationally defined as a set of specific heart defects that are associated with impaired oxygen circulation. Dr. Oster is far better informed on this. I took this list from his article on lessons learned. So, I will defer to him for any questions.

About 2,000 babies in the United States are born each year with recognized CCHD, of which 3- to 400 die in infancy. The CCHD was added -- was recommended by this committee in 2010 and added to the RUSP in 2011.

As you all know, states decide which conditions to screen and how to screen, so if states have chosen different policies and adopted them at different times, that variation in states' practices is a form of natural experiment, which can be evaluated by comparing the states which have adopted different policies at different times. As you all know, the screening is currently done using a point-of-care

pulse oximetry test.

So, our objective is to estimate the effect of state CCHD newborn screening policies on infant deaths from congenital heart disease, both CCHD and all CHD. We -- the method we use is a technique called difference-in-difference analysis, which is probably unfamiliar to most of you.

If you're familiar with pre/post evaluation design, where you are having pre/post, before and after policy or intervention, and you're comparing those which had intervention and a matched group which did not have intervention, this is an extension of that using time series statistical methods, where you're not having a single group, but you're looking at many points in time, and you're doing multiple regression analysis to control for other factors that might be accounting for some of that variation. This is a method which has become very popular in economics as a way of evaluating policies.

The method assumes that you have a

similar pre-policy trend in areas which adopted the policy and those which did not. That's a -- You have to do a statistical test to see, is that hypothesis consistent with the data after controlling for other factors that might also be influencing the outcomes.

The data source -- we used the period linked birth-infant death data files from the National Center for Health Statistics from 2007 through the end of 2013. We used data on births through the middle of 2013 linked to deaths through the end of 2013. We're looking at deaths through 6 months of age with the assumption that that is the period of time in which early detection of CCHD could influence the survival, and we excluded deaths during the first 24 hours because, in the United States, the recommendation is, the screening is done at approximately 24 hours. So, obviously, screening could not influence, causally, deaths before 24 hours.

We looked at the count of infant deaths specifically coded on the death certificate as

CCHD, those 12 defects using the ICD-10 codes, and we also looked at other CHD, the majority of which have a code for unspecified CHD. But you don't know what the defect is; it's just quoted CHD, defect unknown.

The data are grouped by state of birth and the month/year, so the number of deaths of infants born in a state during the month in which a screening policy was in effect. We then look at all of their deaths, up to 6 months of age, after 24 hours, classified by what the screening policy was at the beginning of that month.

So, we classified state screening policies in mandatory and non-mandatory, but the mandatory -- There's a key distinction between a mandate which has been adopted, either by legislation or regulation, and one that's been implemented at the provider level. There's typically a lag period. That lag can be as long as 2 years between when a mandate is adopted and when it takes effect at the provider level. So, we have mandates that have been implemented,

mandates that have been adopted but not yet implemented, and then voluntary screening policies, then use the Poisson regression model of the numbers of deaths to a given cohort, take the natural logarithm of that number, and adjust it for state factors and regression analysis.

The states first adopted CCHD screening policies in mid-2011. Eight states implemented screening mandates by June 01, 2013. Two early adopters, August 2011, January 2012 -- and here's -- Well, this is not a good formatting, I'm sorry, but -- Six implemented mandates during July 01 to June 01, for a total of 8, then 13 other states had adopted mandates but not yet implemented them. So, they were classified as not mandatory for the purpose of this analysis. Five states had adopted voluntary screening policies, which hospitals were encouraged to screen, but there was no accountability in place.

So, we'll skip over this list. Then, we classified states -- the birth months, by all states: states with no policy implemented, states

with mandatory policy, and states with voluntary policy. In this case, the mandatory policy includes when the mandate was -- before it was adopted; after it was adopted, before implemented; and after implementation.

So, if you look at that middle group, it's quite interesting. These are crude, unadjusted differences. What you see is that -- There are a couple of things: 1) The states that adopted mandates had lower CCHD death rates before they adopted the mandates. No surprise. Early adopters tend to be those that have already done more before the policy's adopted.

But what's more interesting is, if you look at that period before adoption and after adoption but before implementation, there's essentially no change. The big change occurs after it's implemented, after the date at which hospitals, birthing centers, are told they have to screen. Then you see the big difference, about a -- almost a 50% lower CCHD death rate in those months.

And what's also surprising is the other CHD. There's about a one-third lower death rate after implementation. And then, if you look at the states with voluntary policy, what do you see? It's a wash.

So, then we did our complicated statistical analysis. I'll spare you the details, no tables of regression coefficients. The summary: After adjusting for all other factors, including the time trend, there was one-third lower number of CCHD deaths in states after a mandate was implemented compared to other states and other time periods. And other CHD deaths fell by one-fifth, 21%. Both changes were statistically significant. Non-mandatory screening had, essentially, no effect. Differences were less than 5%, between zero and 5%, and no statistical significance.

We extrapolated these findings, assuming that all 4 million births in the United States each year, roughly, would be in states with screening mandates. We calculated that there

would be a reduction of 120 recognized CCHD deaths per year and 117 other CHD deaths. There's more CHD -- other CHD deaths than CCHD deaths. So, there's a smaller percentage reduction in that other CHD category, but the absolute numbers are comparable.

We suspect that many of those other or unspecified CHD deaths were actually unrecognized CCHD, which were never recorded as such. Others, there may also be an effect of early detection on deaths from other defects. We cannot distinguish that with these data.

Discussion: What are the implications? Back in 2011, when the secretary added CCHD to the RUSP, CDC was directed to do a cost effectiveness analysis to help states understand the implications. I was involved with that. Cora Peterson, a health economist, was the -- the lead -- led that analysis, published the results in 2013. Approximately $40,000 per life here saved, which is generally considered cost effective. That analysis assumed that screening 4 million

infants per year would save 20 deaths. If universal screening avoids 120 instead of 20, obviously screening is much more cost effective than was projected, and that's not even taking into account the possibility that there's -- more than 120 deaths would be avoided.

Limitations: the small numbers of months after which mandates were in effect. We used the most recent data that have been made available to us, the 2014 linked birth-death by all has been requested, and we will do additional analyses once we get access to those data.

And also, I should mention a limitation that we don't have access to actual screening practices. We know that some states have adopted CCHD screening without any state -- official state policy. There were a couple of states we considered excluding a couple jurisdictions where we knew that -- or we had been informed that most hospitals were screening, even though there was not a state policy, but we -- and we decided not to do that ad hoc adjustment. So, this is a

conservative analysis.

I would like to acknowledge my co-authors, especially the lead author, Rahi Abouk, who's an academic economist who specializes in doing difference-in-difference analyses of various types of health policies and approached me to ask if I'd be interested in collaborating with him on this analysis, and my other two colleagues, Elizabeth Ailes, a birth defects epidemiologist at CDC, and Dr. Matt Oster, who will be coming up next. Thank you.

(Applause)

DR. JOSEPH A. BOCCHINI, JR.: Thank you very much, Scott. We're going to hold questions until the second presentation and then bring Scott back up to the podium.

So, our next speaker is Dr. Matt Oster. Dr. Oster is going to make his presentation by telephone. He is a pediatric cardiologist at the Sibley Heart Center at Children's Health Care of Atlanta. He holds Emory appointments of associate professor of pediatrics in the school of medicine

and associate professor of epidemiology in the School of Public Health, as well as an appointment as a medical officer in CDC's National Center on Birth Defects and Developmental Disabilities.

So, welcome, Dr. Oster. You are ready to go.

DR. MATT OSTER: Great. Thank you very much for the invitation. I'm very happy to present a -- a clinical perspective of critical congenital heart disease screening, the concerns, challenges, and opportunities from the clinical perspective. I apologize I was not able to join you all in person today as I am on clinical service this week.

All right, next slide. So, first I'm going to address some of the concerns. When screening was added to the RUSP, there were a lot of concerns from the cardiology and general pediatric community about, you know, first, do we really need this? We're already capturing a lot of cases. Hospitals were wondering how we're

going to pay for this and who's going to pay for it, and, finally, you know, will this overwhelm the system? Are we going to, you know, be burdened with all these cases that we're finding that may or may not be real?

Next slide. So, first the question of, do we really need this, and I mean, this question was actually posed to me by some cardiologists up in Boston, who were saying, "We have so many cases who are prenatally diagnosed. Is this really going to add much?"

And, you know, this got me thinking about, well, what is screening for critical congenital heart disease. We talk about pulse oximetry, but really, I think of it as a number of different spots in the process. You know, first, antenatally, so the prenatal ultrasound or other prenatal screening, genetic screening. We can certainly find heart disease cases there. After the baby's born, there's the newborn physical exam, and so if we detect any signs or symptoms in the first 24 hours -- You know, just

the -- the exam itself is a screening test looking for any problems, and then, finally, the 24 hours with the pulse oximetry, which is what we're talking about today.

Next slide. So, I worked with Elizabeth Ailes and some others at CDC to figure out, what exactly are the numbers. So, you know, we pulled a number of different articles to look at a number of the different defects of congenital heart disease -- of critical congenital heart disease to figure out, when are they being diagnosed and what is the potential impact of screening here.

And, you know, we realized, okay, prenatal diagnosis -- about a third of CCHD is found that way, but that ranges from about 5% to 56%, you know? Five percent on a low end, really, for total vein -- total anomalous pulmonary venous return, and 56% for hypoplastic left heart syndrome, which is a little bit easier to see on a prenatal ultrasound just because of the discrepant size of the ventricle. Seeing

anomalous veins is very hard to see on a prenatal ultrasound.

And then, once kids are born, how many, you know, are timely detected versus late? Well, another -- add 40% if timely detected, but that leaves about 30% of kids who are still being detected late, and, you know, again, the total veins kids and then a lot of kids who have coarctation of the aorta were being detected late.

And then, we said, "All right, well, knowing what we know about the defect and the different sensitivity and specificity of this -- of pulse oximetry for each defect, how many of those are going to be detected by screening? And it's around half -- actually a little bit more than half -- but around half is what we estimated. And this number is going to be about 900 kids that could be found by screening positive. We might still miss another 8- or 900 kids due to false negatives.

And this was -- you know, the -- the

largest percentage here is going to be that total anomalous pulmonary veins that I mentioned. That's very hard to see on prenatal diagnosis. It can be completely asymptomatic in the first 24 hours of life. It does not typically have a murmur. And so, it's kind of a poster child for critical congenital heart disease screening using pulse oximetry.

On the other hand, coarctation of the aorta -- many cases will be missed, but it will also be the most commonly found just by the nature of that it's the most common defect. So, we thought, yes, this is actually going to make a difference and we do need this, and people responded well to it.

Next slide. How are we going to pay for this? Well, as you heard Scott mention, you know, when we did the analyses looking at the cost effectiveness, people quickly realized that, yes, this is cost effective, and this is something worth doing, but there were concerns about, would this be a separate charge, are the states going

to pay for it, what's going to happen.

Really, what's happening is just, the hospitals are just including this as part of their overall standard newborn care. It's not a separate charge, it's not a separate thing, just for the test itself. Now, if further testing is indicated, such as an echocardiogram or an X-ray or other things, that's just being billed and paid for the same as it would be for a symptomatic child. This issue's kind of been put to rest.

But the last concern, and this was actually a very big one when this came out, was, will this overwhelm the system? I gave many talks to nurseries and pediatricians, and a lot of people had a concern over, this is going to delay discharges; we're going to hold up getting the families home.

Well, it's actually quite rare since the vast majority of kids pass screening, and the biggest part of it, though, is that parents and the clinicians aren't really upset. Parents

understand that if their child's being delayed, it's for a reason, and they definitely want to be safer than sorry, and they understand when things do get delayed so you can get further testing. That has not been an issue.

Would this be an excessive burden on pediatric cardiologists? And in our own group, a lot of people were initially upset, because they thought they'd be getting these 3:00 a.m. phone calls to go to an urgent echocardiogram and a cuedoo (phonetic) probably, as well, but we worked with nurseries and others to come up with a protocol that if a kid looks good, that could wait 'til daytime.

And I talked to other places around the country, and people say that this really hasn't made any huge blip on them. It's not been a huge burden causing excessive echocardiograms. They still get calls much more frequently for other things, such as murmurs or other concerns. So, screening has not been an excessive burden.

And then, what about unnecessary

transports from remote hospitals who might not have the means to evaluate a child? That is exceedingly rare. I'm not going to say it doesn't happen, but it exceedingly rare, and I'm going to raise the point here about, what exactly is unnecessary, and we're going to talk about that a little bit later.

So, what have been some challenges in implementing -- all right, next slide -- regarding the pulse oximetry screening? So, these -- these are three of the biggest challenges. So, first, what does a negative result mean, why are we still missing some cases, and how do we adapt it to special settings?

So, next slide. I listened for a bit yesterday, and I -- I know there was a long discussion about what exactly does a negative screening mean, and how do people interpret this, and I had this concern that pediatricians were going to rely on screening as replacing current standard of care rather than being an addition.

And this is a letter to the editor that

was published shortly after screening started becoming widely accepted, and it's titled "Misinterpretation of Negative Pulse Oximetry Screening," and the -- seemed like things were on the right track, and then the authors purposely omitted -- it had this sentence in there, saying that: We urge the American Academy of Pediatrics to mandate that nurseries document the cardiac conditions specifically ruled out by virtue of a negative screen on every discharge summary.

And that's not an isolated thing that I heard from people. There was a pediatrician in the community here who once told me that, "Oh, I saw a 1-week-old who had poor pulses. I was worried about a coarc, but then I saw that the child passed the screening test, and I felt reassured." That is a myth that we have been trying to dispel.

Next slide. So, as part of that, I and a couple other clinicians at CDC wrote this response to that letter, where we said that until there's a screening test for CCHD that has close

to a hundred percent sensitivity, we believe that pulse oximetry screening should be used as one additional tool to detect CCHD, but it should not preclude routine clinical examinations, nor should it be used to rule out heart disease, including any type of CCHD. This is all just ramifications of screening being -- of pulse oximetry being a rather low sensitivity for a, you know, standard screening test, and it's really just one more tool at our disposal.

Next slide. But if we're still missing cases, why is that? So, as I said, the sensitivity is pretty low compared to others, really about 50- to 75% depending on what definitions you use to count critical congenital heart disease, the biggest one being coarcs. Do you count them or not? I tend to say yes, just because they are the most common, and we do pick up a number of them. When you add it other things at our disposal, you get the -- the overall sensitivity of just detecting CCHD to 85%, like I showed on that initial slide from Elizabeth

Ailes' study.

And, you know, part of it is just the nature of the test itself. There are various determinants of hypoxemia that vary from condition to condition and even from child to child within the condition.

First, there's the timing of the test. You know, how have the hemodynamics changed in other parts of the world? Like, in England, they test early, at 6 hours. We tend to test it a little bit later. There's differences in the flow across the PDA; how does that change. Is the PDA even open, or is it closed yet? And then the severity of the disease. So, these are all things that are, really, kind of out of our control to some point, especially the physiology.

But there's a lot that's within our control, and human error does lead to a number of cases missed. Next slide. So, why are we still missing some cases? All of these, I have instances and anecdotes that I've heard of, of kids being missed.

First, the timing of it -- I know there was a child here who, you know, had an indeterminate result, and instead of being tested an hour later in one of the nurseries around here was tested 12 hours later, passed it -- I'm not sure if testing earlier would have picked the kid up or not, but hopefully, it would have prompted evaluation. The kid eventually passed it, went home, and ended up having hypoplastic left heart syndrome and was not a survivor.

Equipment -- Equipment malfunctions can happen, and are people using it right.

Algorithm interpretation -- This is a big one. People were misinterpreting the algorithm, specifically the 3% and what true fail or rescreen or whatnot.

And then, echocardiography -- First, just the availability of it, but then also the ability to perform it appropriately. We had another case here in Georgia where a child failed a screening, was at a remote hospital. They didn't have pediatric echosonographers available, but -- but

the way that it is set up is, they have adult sonographers do the test, and then pediatric sonographers at our hospital interpret it. All the pictures that were obtained appeared that things were good, but the -- the sonographer did not get a great look at the veins, and so total veins was missed on that echo.

Fortunately, that child presented later, and an astute pediatrician said, "I know this kid passed, but I still think something's wrong," and sent them in for a -- a good pediatric echo and it was picked up, and that child did well.

Next slide. Another big area, though, is, how do we adapt to special settings.

So, first, altitude -- On this graph, you see, going from left to right, that there is, you know, increasing degree of altitude, and as that goes up, you have decreasing saturation levels. So, different hospitals, and especially led by a number of places in Colorado, have been trying to adapt to their areas.

I do know that one hospital has even just

stopped screening, though, because a third of the kids were failing, and they're really trying to figure out, how do they modify this algorithm, from the timing of it, or do they lower the thresholds, what do they do. There's still work that needs to be done here.

Next slide. Another big area is out-of-hospital births. This graph is actually from a group in the Netherlands who have kind of been leading some of the efforts here, but there is certainly still a concern in many parts of the United States. And basically, what they have done, though, is said, "We can't stick around for multiple hours to repeat tests," so they just repeat the measurement after 1 hour rather than -- and just do 1 repeat measurement rather than 2. So, they've modified the algorithm that way.

Let me tell you, in Pennsylvania, I recently heard a presentation from a group there that said -- they don't really call it CCHD screening there, with their midwives. They call it hypoxemia screening, because there are a lot

of other conditions picked up, and I think that's a good approach to get different populations to buy into it.

Next slide. In the NICU, though, that's also been a very big area. So, you remember pulse oximetry screening was recommended and designed for newborn nurseries. Yet, in some states, specifically New Jersey, who's been kind of a leader on this, the legislation was written and enacted that -- that all children need to be screened using pulse oximetry, regardless of whether they're newborn nursery or NICU or wherever.

So, this graph is actually from a group in China, who published their results last year, saying, "We found a hundred percent of kids with CCHD with a hundred percent of sensitivity." Well, that's good, except that, if you see the highlighted box here, 56% of the kids who were tested had a positive test and, you know, had to go on to further evaluation. So, that's not really useful for screening.

But recently, just last week, the group here in New Jersey and a few other states who are collaborating, they have come up with a modified protocol and recently published their experience as to how they can adapt this to meet their needs in a NICU. Now, they didn't detect any new cases they didn't already know about from prenatal or symptomatic evaluation, but they have been able to come up with a system: Well, what do we do with a child that's on oxygen, and what do we do with a premature baby? And this is something that I think will be used in NICUs, now, going forward.

Next slide. So, what opportunities are still available in the -- with pulse oximetry screening? Some things that are still being figured out are: what algorithm to use, what do we do with false positives, and is there something better than oxygen saturation level.

So, first, what algorithm do you use? You've seen this picture -- I believe, back in May, it was presented -- just reminding you that

there are different algorithms used depending on where you are screened in the United States. The AAP algorithm you're all familiar with, also known as the Kemper algorithm, is the most widely used.

New Jersey, when they implemented, said, "Well, we're going to -- so instead of mean to mean 95 or higher in either the hand or foot, we're going to do both." So, what that does is, it's going to catch everything the AAP one would, plus, maybe, a few more cases. So, it has a higher sensitivity but you'd also expect, potentially, a higher false positive rate.

Tennessee came along and said, "Well, it's exceedingly rare for the foot to be higher than the hand, so if the foot is 97 or above, we'll make the reasonable assumption that the hand is also 97 or above" -- which would pass under the normal protocol -- "so we'll just start with the foot and then go to the AAP protocol if we have any issues."

So, a couple of years ago, I collaborated

with two people at CDC and Georgia Tech that collects data from a lot of places -- Sorry, next slide -- to collect information about what was being done. And we ran it through all these algorithms, plus, we actually did modifications to all these, trying to change the cutoffs and the difference and -- There was about 1,800 different algorithms, but these are the ones that kind of rose to the top.

And the take-home points here, though, are, with the different algorithms, including, even, just a simple one that we just threw in there, that if you just did one saturation of 94% or 95% in the foot and called it a day, with the different algorithms, you have similar sensitivity with all of them. The difference, though, is the false positive rate, or the one minus specificity, and that's going to vary quite a bit, from a .2% to just over 1%, depending on what you're looking at.

Next slide. We've also -- This is fresh data from a hospital here in Georgia that does

about 18,000 deliveries a year. This is their first 4 years of screening, and what were their results. And, you know, there are 77,000 children. About 17 failed right away for a low saturation less than 90. The vast majority passed. But then, 172 had 1 repeat screen, and then another 23 had a second repeat screen. And of those, 14 were still in that indeterminate range and were considered fail and added to 31.

Well, we've gone back and looked at those nine that, kind of, had the third screen and were then considered a pass, and we're really kind of raising the question of, do we really need to have the second repeat? Could we just do one repeat and then call it a day?

And part of that is because it's not a huge number that we're eliminating here. Part of the rationale for that second repeat was to decrease the false positive rate, decrease the burden on cardiologists -- which has not been a big issue -- decrease the burden on the delayed discharges -- again, which has not been a big

issue. So, what are we really getting with -- with that second repeat screen, and what are we potentially losing?

And next slide. So, what we may be losing, though, is this -- this false positive, and what we've noticed and others have noticed, as well, is that about up to 70% of the, quote, false positive cases might have some other explanation about hypoxia, which is important to take care of, such as pneumonia, hypertension, pneumothorax, sepsis, meconium aspiration, or in transit to get near the newborn requiring oxygen. These are all important conditions that we want to identify and treat and are considered, you know, additional conditions that we're finding beyond just critical congenital heart disease.

Next slide. So, we raised this question -- this is in that same article last year, about lessons learned -- about, what do we do with these false positives. And we've provided some new guidance now to clinicians, saying that additional evaluation and testing of the infant

should be prioritized according to the conditions most relative -- most relevant for each case, and such evaluation should not be delayed while awaiting an echocardiogram. The child should not be discharged without resolving the cause of desaturation, or at least before excluding potentially life-threatening conditions.

And then, we added: If a cause other than CCHD is identified and appropriately treated -- such as sepsis or pulmonary hypertension -- with resolution of hypoxemia, an echocardiogram might not be necessary. And this was really a recognition that there are other important conditions, and we don't want to delay the evaluation and management of those conditions just because an echo might not be easily obtainable.

So, next slide. Is there something better than oxygen saturation level? You know, we're missing a lot of cases just looking at saturation, and so, you know, hopefully, though, we can find something that can -- that can detect

some of those other cases, particularly the left-sided obstructive defects, such as coarctation of the aorta.

So, perfusion -- and this is something you've probably heard about -- has been tossed around. These images just show that it can be detected from the waveforms of pulse oximetry, but I'll draw your attention that these are from a article by Anne de-Wahl Granelli from 2007.

So, here we are, 10 years later, and perfusion index still is not quite ready for primetime. It just has some overlap, and some of it's hard to capture. People are still looking into it. Hopefully, one day, it may be useful, or hopefully, something similar to it can be useful to try to identify coarctation of the aorta or other left-sided defects.

Next slide. Conclusion -- So, in conclusion, there were many fears and concerns when pulse oximetry rolled -- rolled out. People are often afraid of change. But those initial concerns have, for the most part, been allayed.

People are very accepting of this and recognize the value of it.

However, there are still some challenges to fully implementing the screening process, notably: making sure people understand that it doesn't rule things out and then, also, some of the special settings, particularly altitude, in those areas.

But then, finally, opportunities still exist to improve CCHD screening further. Hopefully, one day, we'll have something beyond pulse oximetry that can help detect some of those important cases.

We -- I'll just end with this one last anecdote. Just last month, I was on call, and there was a 7-month-old child who came in for about her third respiratory illness of her life, and her very astute mom said, "I want you to check the heart, because there's just something wrong with the heart." So, the general pediatrics team got an EKG that we saw was very abnormal, and we had an echo. The heart function was very

bad, and that child had a pretty severe coarctation. Fortunately, we were able to correct that, and now the child's doing well at home.

Next slide. Thank you very much for your time and attention, and I'll be happy to take any questions.

DR. JOSEPH A. BOCCHINI, JR.: Thank you very much, Dr. Oster. That was a really nice presentation.

So, we've had two really good, strong, great presentations, so let's bring Scott back up to the podium, and let's open this to questions and comments from some of the committee. First -- first Joan, and then Cathy.

MS. JOAN SCOTT: Thank you, both of you. This was a really good part 2 to some of the conversation that had -- and presentations from in May.

And one of the things that I'm remembering from that presentation that was surprising is the -- is the gap in information that's being collected at the hospitals and

that's going into state newborn screening information systems to try and collect what's being done, how is it being done, to also give a more boots-on-the-ground picture of where there might be gaps and opportunities to improve the system.

And I was wondering if either one of you had any thoughts about the role of that, and would that be -- if there's ways that we can help there.

(Off-mic speaking)

MS. JOAN SCOTT: Sorry, Joan Scott, HRSA.

DR. MATT OSTER: Great. I can talk about that briefly.

You know, I showed you the results from that algorithm project that we did, trying to optimize the algorithm and what would different algorithms look like. And one of the biggest challenges we had, though, was getting useful data to look at that. A number of states were just collecting, first of all, was the screening done. Some were collecting just pass or fail. But

we've shown and we know that a number of times, that's misinterpreted. Even in the best scenario, it's not always appropriately interpreted.

So, those states that are collecting the actual number values and what the outcomes were, were very helpful in -- for a number of ways: 1) just improving the quality and giving feedback to hospitals that might have some issues with interpretation, and then, second, for us trying to optimize the algorithm and come up with ways to improve screening further.

I understand it's certainly a challenge, and different states need to do what they can do, but some states that have added the pulse oximetry screening with the values and the outcome on the birth certificate, I think, have been leaders in the data collection effort.

DR. SCOTT GROSSE: Last year, CDC had a Public Health Grand Rounds, Beyond the Blood Spot, about point-of-care newborn screening for hearing and CCHD. The presentations are archived on the CDC website.

Dr. Sontag, Marci Sontag, was one of the presenters, and one of the issues that came up was the disparity between EHDI, where there are a lot of resources for public health surveillance by state health departments, and CCHD, where those such efforts are not widely adopted because of lack of specific funding. And so, we -- the -- the presenters discussed those various issues and the potential benefits of having state surveillance, and integrated with birth defect surveillance.

DR. JOSEPH A. BOCCHINI, JR.: Cathy?

MS. CATHERINE A. L. WICKLUND: Yeah, Cathy Wicklund. Thank you for this presentation. I had a question, and I apologize if you guys covered this, but what were the state-specific factors that you integrated into the -- the regression, and -- and how did you guys determine those?

DR. SCOTT GROSSE: The -- Primarily, they were state fixed effects --

MS. CATHERINE A. L. WICKLUND: Okay.

DR. SCOTT GROSSE: -- so that's -- that -- it's, like -- So, anything that was constant in a state over time was controlled through a state fixed effect dummy variable. We had time-specific dummy variables. Then, also, there were time-varying state variables, things like the unemployment rate, the demographic composition of births. Those factors didn't explain very much. The -- the state fixed effects and the time fixed effects -- because there was a downward trend in CHD deaths over this period of time. Those are the primary reasons why there was a difference between the unadjusted and the adjusted differentials.

DR. JOSEPH A. BOCCHINI, JR.: Melissa.

DR. MELISSA PARISI: Thank you for those really nice presentations. I had a question about the reduction in the non-CCHD CHD deaths, and I know that your analysis, Scott, may not be granular enough to tease some of that apart, but I wonder if, in addition to the fact that some of the -- some of the kids with actual CCHDs were

not picked up because of, you know, the lack of sensitivity for the pulse oximetry screening, if there might also be an effect of, just, increased awareness of congenital heart disease in newborns that might have somehow caused the clinicians caring for these newborns to just be more alerted and -- and aware of potential signs that might suggest a congenital heart defect, and that was somehow contributing to earlier detection.

DR. SCOTT GROSSE: That's a great suggestion, and we agree. We are not analyzing the effect of pulse oximetry screening. We are analyzing the effect of a state mandate requiring providers to screen infants for CCHD. And, undoubtedly, part of the reduction is due to the greater clinical awareness. Thank you.

DR. JOSEPH A. BOCCHINI, JR.: Annamarie?

MS. ANNAMARIE SAARINEN: Thank you for those great presentations. Annamarie Saarinen, Newborn Foundation, and I would feel badly if I didn't get to comment on this subject matter.

FEMALE SPEAKER: We're waiting.

MS. ANNAMARIE SAARINEN: Yeah, I know, you guys were waiting. So, since this is on the record, I'm asking this, almost, as a point of clarification, but I -- Sometimes these statistics get muddled in my own head despite the number of presentations I do on this subject, as well. But per the CDC website and most of the other congenital heart defect advocacy organizations, I just wanted to be clear about the numbers you started with, which were -- and it might be just a little bit of nomenclature, but the number of annual deaths attributed to critical congenital heart disease and contributed to congenital heart disease.

I know the basic understanding is that approximately 3,000 deaths a year are attributed to congenital heart defects, whether that's serious category or critical category, and that's in infancy, so under 1 year of age. So, I just wanted to know what, statistically, we're looking at. And it's 4.2% of all neonatal deaths attributed to CHD.

DR. SCOTT GROSSE: There's been tremendous reduction in the number of infant deaths from CHD in recent years. There have been multiple publications which have tracked that. We were using the linked birth-infant death records, and so from 2010 to 2013, we saw, even within that period, a fairly large reduction in the number of infant deaths due to CCHD and other CHD. The 3- to 400 is referring to the most recent time period, since 2010.

MS. ANNAMARIE SAARINEN: Okay.

DR. SCOTT GROSSE: And that's for the -- the ICD-10 codes associated with those 12 specific conditions.

MS. ANNAMARIE SAARINEN: Yeah. I think that's -- it's -- it's tough data, you know, to work with when you're dealing with just coding, because --

DR. SCOTT GROSSE: Yes.

MS. ANNAMARIE SAARINEN: -- we all know that things get --

DR. SCOTT GROSSE: Yes.

MS. ANNAMARIE SAARINEN: -- coded in different -- in --

DR. SCOTT GROSSE: Correct.

MS. ANNAMARIE SAARINEN: -- different places, but I always appreciate your conservative approach.

DR. SCOTT GROSSE: And, also, I would like to -- The one person in this room who is not surprised by our findings is Annamarie.

(Laughter)

DR. SCOTT GROSSE: When we talked about this several years ago, she reacted to the numbers we were using in that cost effectiveness analysis as being very conservative in terms of the number of deaths avoided. It was -- we were probably off by an order of magnitude, and these new findings actually confirm her expectation.

MS. ANNAMARIE SAARINEN: Well, thank you for doing further analysis, and I'll look forward to -- Once you have your 2014 numbers, that'll be great to see, as well.

And better data collection -- I know I

sound like a broken record on this, but to the degree that can be improved and that this committee can support that for providing, sort of, some best practices and guidance for hospitals and systems that have then incorporated it to electronically transmit actual values to the state newborn screening programs -- I -- I just -- There's just no other possible way we can measure the impact and outcomes for these kids than that.

DR. JOSEPH A. BOCCHINI, JR.: Thank you. Dr. Watson?

DR. MICHAEL WATSON: So, I'm curious about the diagnoses, not the clinical diagnoses of the heart abnormalities themselves, but there's more and more work going on identifying genes associated with congenital heart disease. The committee has had deletion 22 brought to it before as a potential candidate for newborn screening.

So, I'm just curious about, are there -- across the diagnostics, or the etiological causes

of the heart defect, are there any more common -- They're really hard genes to predict from, so I don't -- I doubt it would be great candidates on the front end for sequencing, but I'm just curious about the diagnoses -- or etiology of the heart defect.

DR. MATT OSTER: Yeah, this is Matt, and I can -- I can chime in on that. So, as you mentioned, DiGeorge syndrome, or 22q11 deletion, is certainly one of the most common. Other ones that we see commonly, particularly, include trisomy 21 with AV canal, which is technically one of the CCHDs, so it is an important thing we look for.

Beyond that, a lot of them are just very multifactorial or rare. It's -- it's more, kind of, the opposite. You know, when we look for certain cases of heart defects, if we find other associated things or other things, we'll send a chromosomal microarray because we think something might be up, or if it particularly looks DiGeorge-ish or one of the DiGeorge conditions,

we'll send just a fish for 22q.

You know, I would -- I would love to see that we have some sort of easy way to detect certain -- know certain genes and find those; it's just -- it's not to the point, yet, where I think we're ready to do that and have certain things identified. Hopefully, in the future, we'll identify some more, I guess, smoking guns, if you will, but it still remains quite multifactorial.

DR. MICHAEL WATSON: So, in your cost effectiveness study, did you -- would you -- would you have excluded a Down syndrome baby, for instance, that presumably should have been recognized as having something going on in the -- at birth so was not really, you know, the asymptomatic --

DR. SCOTT GROSSE: I don't think we excluded Down syndrome, but I don't think CCHD is particularly common with Down syndrome.

DR. MICHAEL WATSON: No, the AV.

DR. SCOTT GROSSE: They have other

effects.

DR. MICHAEL WATSON: Right. Yeah.

DR. JOSEPH A. BOCCHINI, JR.: All right. Matt?

DR. MATT OSTER: Yeah, nothing to add there. He -- he said it right.

DR. JOSEPH A. BOCCHINI, JR.: Carol Greene?

DR. CAROL GREENE: Well, just to add for the Down syndrome, between 30- and 50%, most estimates 40%, of babies have a heart defect; so, those babies will be looked at differently.

In a recent paper -- I think it's quite recent -- when you put together the baby -- roughly 70% of babies had isolated heart defect, and some of those would be multifactorial, some of those would be single gene. Most of the genes we don't know. Thirty percent of the baby had either a syndrome or multiple malformations, and one of the things about finding a baby with a heart defect is, you might not -- it -- it might be the heart defect that leads you to look for

the other malformations that are internal that you didn't even see, so -- But, yeah, it -- it would be --

What I wanted to say is, first of all, this is -- is fabulous, great news. It's good to hear that we are making a difference in -- that -- that newborn screening is making a difference and that it can be measured. That comes back to all the ways that we talked about more data and measuring things.

And the other thing that I wanted to say, besides that it's great news, is that it is -- I mean, this group is pretty conservative, and I think with justice, and it is great to hear that it's making an even bigger impact than was anticipated, and that might lead to consideration of looking at -- at ranges or windows.

And the other thing I wanted to say is that this is fabulous making an impact, and still we're discussing that we need to make improvements, and -- again, Carol Greene, SIMD -- is, we -- we don't have to have everything

perfect, every duck in a row, before we're ready to go forward. We're making a big difference in saving people's lives, and we're still trying to tweak the protocol and make it better. So, we don't have to have every bit of everything known before we're ready to move forward.

MS. ANNAMARIE SAARINEN: May I ask a follow-up question on that? And that was even before you said what you said, Carol, so thank you. Annamarie Saarinen, Newborn Foundation.

Is it generally the role of this committee to -- to look at those, sort of, process improvements? So, if you were going to modify a -- a cutoff or, in this case, a protocol for a point-of-care screening, is that, sort of -- Once we've done that early work as a committee, does it move over to, okay, the AAP and the CDC are going to do evaluation and maybe publish another paper with recommendations on those sorts of changes?

Per what Dr. Oster said about the -- the second, sort of, rescreen potentially -- I -- I

personally think not necessary -- but potentially not being necessary, how -- do we -- do we weigh in on that substantively with any of the conditions that we review?

DR. JOSEPH A. BOCCHINI, JR.: That -- Certainly, it depends on the -- where the expertise is for making those kinds of changes. In the Laboratory Standards Group, certainly, they have looked at making recommendations for changes in the way testing is done or what analyte is used, based on evolving data and their input, to -- to -- to make a change.

And so, yes, the -- part of the responsibility of the committee is to evaluate where we are, what's being done, and to see if changes need to be made, and -- and then help support those changes based on the expertise involved that's needed to make that happen.

So, that is under the purview of the committee, and part of the reason we want to see what we're doing and what the outcome is, is to just get that and -- and as Carol indicated,

sometimes you don't really know exactly what's going to happen when you start something, and so hearing back as to what has happened and then adjusting things or modifying recommendations is always really important. So, yes, it is under our purview. Yes.

MS. ANNAMARIE SAARINEN: And -- and what's the mechanism, like, from Kellie's group or whatever -- What is the mechanism for getting those recommendations out there? You -- you don't send another letter, for instance, to -- How do -- How do we get those out to the state programs and the world?

DR. JOSEPH A. BOCCHINI, JR.: Well, the last -- the recommendation that was made -- and, just, you all have to remind me -- it was to change the analyte for tyrosine for --

(Off-mic speaking)

DR. JOSEPH A. BOCCHINI, JR.: And -- and that went out -- Go ahead and -- Kellie, and give us --

DR. KELLIE KELM: It was -- Well, and

actually, I think a lot of the work started with -- Was it the CDC started that work? Carla?

DR. CARLA CUTHBERT: Yeah, that -- that was looking at tyrosine and -- certainly, at the -- the importance of succinylacetone as a marker, and --

DR. KELLIE KELM: The tyrosine was -- That's another conversation, though, because obviously, for most conditions, we don't do an extensive review of methods, et cetera, and -- and obviously, what we're -- what we are nominating is that we are screening for a condition, not always how, although for CCHD, I think, that was a place where we wound up having working groups that were formed by -- as an offshoot of this committee, with other people, and came in and then they, obviously, had the publication, you know, that included the Kemper protocol, right? But that was pretty atypical.

If you look at, obviously, a lot of the other, more recent things, like SCID and MPS1, et cetera, we didn't do that. So, I'm not sure if it

was just that we felt that there needed to be more information provided for that one screening to go forward that people felt was, sort of, missing -- But we don't often -- We often talk about techniques and methods but don't necessarily talk about an endorsement or --

And I think for the one condition that we talked about, it was an actual safety issue, where we also knew that some states were hanging onto tyrosine, and that we felt that a strong statement needed to be made, so.

FEMALE SPEAKER: Right. You could have been screening -- having -- you could have had tyrosine as a marker but still possibly miss tyrosinemia type 1 cases, and it was just really indicating that succinylacetone was a, by far, much better marker for that disease.

DR. KELLIE KELM: But -- Kellie Kelm. In this case, since this committee had a workgroup and had publications, I think if -- that would be something we would need to think about, about how -- if there were changes to be made, since it was

-- the CCHD was -- was special in that way.

DR. JOSEPH A. BOCCHINI, JR.: Jeff?

DR. JEFFREY P. BROSCO: Jeff Brosco. I just want to point out that the Follow-Up and Treatment Workgroup is looking for new projects, too, and so this may fit into that, as well, so.

DR. JOSEPH A. BOCCHINI, JR.: Other questions or comments?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: Anybody on the telephone?

(No audible response)

DR. JOSEPH A. BOCCHINI, JR.: If not --

DR. CHRIS KUS: This -- this is -- this is --

DR. JOSEPH A. BOCCHINI, JR.: Oh.

DR. CHRIS KUS: -- Chris Kus. The one comment --

DR. JOSEPH A. BOCCHINI, JR.: Go ahead, Chris.

DR. CHRIS KUS: -- somebody had already said was that the -- the financial support for

EHDI is much greater than the other -- well, CCHD, and the question is, why, and what can we learn from that.

DR. SCOTT GROSSE: I'm not -- I -- I can't comment on that. You can go to the CDC Public Health Grand Rounds for some discussion about that issue.

DR. JOSEPH A. BOCCHINI, JR.: Yeah, I don't think we have an answer for that.

All right, other questions or comments? If not, I want to thank both Dr. Oster, Dr. Grosse for their presentations, and I think, as was stated, this was the second portion of our presentations related to critical congenital heart disease, and this was what we were discussing at our prior meeting in terms of, are there data to look at the impact, and we have the data, that -- the -- the beginning of some -- some evidence of outcome. So, that's very -- very good to hear.

So, that brings us to the last item on the agenda: if there's any new business from any

of the members of the committee or others to be brought forward. I guess one of the things that -- - Did you want to --

(Off-mic speaking)

DR. JOSEPH A. BOCCHINI, JR.: Yes, go ahead.

DR. MEI WANG BAKER: So, finally I remember to say my name. Mei Baker. This, I don't believe, is the right time. It just popped to my mind is, just, listen to CCHD, this report -- it make me think about SCID, actually. And I think, next week, we'll have a meeting, in-person meeting, about SCID, so sorry did not ask ahead of time -- how well immunologists that transplant and the newborn screening testing and follow-up large group getting together really to have summary about things that has been put on panel 6 years past, so where we are. And not just matters to get every state to screening, how well we do, what's the -- the outcome. I think that will be -- - I think will be interesting for the meeting report to this committee, and I -- I thought it

would be good agenda item.

DR. JOSEPH A. BOCCHINI, JR.: Perfect, because that was my next question, does anybody have any agenda items that they think would be appropriate for upcoming meetings, and so that obviously is right on target. That's -- Other --

Okay. I guess that's it for now. So, two last things: I think committee members should be aware that -- that HRSA's working on the committee's report to Congress, and we'll be getting that sent to us soon for us to evaluate and provide feedback on that report so that we can complete it, and then, as Annamarie has now invited us all to the meeting -- Just a reminder: It's November 08th and 09th, and we'll see you there, Annamarie.

(Laughter)

DR. JOSEPH A. BOCCHINI, JR.: So, that'll conclude the meeting. I -- I want to thank Catharine for all the work that she did to organize this meeting. We've stayed right on schedule the entire meeting, so I think that's

been really excellent. So, thank you.

(Applause)

DR. JOSEPH A. BOCCHINI, JR.: So, thank you all for attending, and we'll see you all in November. Thank you.

(Whereupon, the above-entitled matter was concluded.)