The Advisory Committee on Heritable Disorders in Newborns and Children

Virtual Meeting

10:00 a.m.

Friday, February 12, 2021

Attended Via Webinar

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Reported by Garrett Lorman

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P R O C E E D I N G S

WELCOME AND ROLL CALL

CYNTHIA POWELL: Good morning, everyone. Welcome to the second day of the February 2021 committee meeting. We will begin by taking roll. I'll start with committee members, Kamila Mistry.

KAMILA MISTRY: Here.

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Here.

CYNTHIA POWELL: Jeff Brosco.

JEFF BROSCO: Here.

CYNTHIA POWELL: Kyle Brothers.

KYLE BROTHERS: Here.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Here.

CYNTHIA POWELL: Carla Cuthbert.

CARLA CUTHBERT: Here.

CYNTHIA POWELL: Kellie Kelm.

KELLIE KELM: Here.

CYNTHIA POWELL: Michael Warren.

MICHAEL WARREN: Here.

CYNTHIA POWELL: Shawn McCandless.

Melissa Parisi.

UNIDENTIFIED MALE SPEAKER: She's on the phone in the audience. We're getting her promoted right now.

CYNTHIA POWELL: Okay, thank you. I'm here, Cynthia Powell. Annamarie Saarinen.

ANNAMARIE SAARINEN: Here.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: Here.

CYNTHIA POWELL: And our organizational representatives, Robert Ostrander.

ROBERT OSTRANDER: Here.

CYNTHIA POWELL: Debra Freedenberg.

DEBRA FREEDENBERG: Here.

CYNTHIA POWELL: Maximilian Muenke. Steven Ralston. Jed Miller.

JED MILLER: Here.

CYNTHIA POWELL: Susan Tanksley.

SUSAN TANKSLEY: Here.

CYNTHIA POWELL: Chris Kus.

CHRISTOPHER KUS: Here.

CYNTHIA POWELL: Shakira Henderson.

SHAKIRA HENDERSON: Good morning, here.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Here.

CYNTHIA POWELL: Jacob Hogue.

JACOB HOGUE: Here.

CYNTHIA POWELL: Natasha Bonhomme.

NATASHA BONHOMME: Here.

CYNTHIA POWELL: Siobhan Dolan.

SIOBHAN DOLAN: Here.

CYNTHIA POWELL: Cate Walsh Vockley.

CATE WALSH VOCKLEY: Here.

CYNTHIA POWELL: Georgianne Arnold.

GEORGIANNE ARNOLD: Here.

CYNTHIA POWELL: And anyone who wasn't able to get through who has joined in the interim? Okay, thank you.

So, we'll begin with updates from the workgroup meetings that were held yesterday afternoon. The workgroups convened to consider processes for the review of conditions on the RUSP and potential updates to the committee's condition nomination form. After their presentations, the

committee will have the opportunity to engage in discussion. Our final session of the meeting will be a panel on innovations in long term follow-up. I'll now turn it over to Mia Morrison, Designated Federal Official, to provide guidance for participating on the webinar.

MIA MORRISON: Thanks, Dr. Powell. Members of the public, audio will come through your computer speakers, so please make sure to have your computer speakers turned on. If you can't access the audio through the computer, you may dial into the meeting using the telephone number that was in the E-mail with your Zoom link. This meeting does not have an all-attendee chat feature. But there was a period for public comment yesterday.

Committee members and organization representatives, audio will also come from your computer speakers, and you will be able to speak using your computer microphone. If you can't access the audio or microphone through your computer, you may also dial into the meeting using

the telephone number that was in the E-mail with your Zoom link.

Please speak clearly and remember to state your first and last name to ensure proper recording for the committee transcript and minutes. The chair will call on committee members first and then organizational representatives.

In order to better facilitate the discussion, please use the raise hand feature, which should be located on the bottom of your screen. Depending on your operating device or operating system, this may appear in a different location.

I'll now turn it back over to Dr. Powell.

CYNTHIA POWELL: Thank you, Mia. First, we have the Education and Training Workgroup chaired by Dr. Jane DeLuca. Dr. DeLuca.

EDUCATION AND TRAINING WORKGROUP UPDATE

JANE DELUCA: Good morning, everyone. Mia, do you have slides, or should I put them up on my end?

MIA MORRISON: They'll be putting them up momentarily.

JANE DELUCA: Okay. Good morning. First, I wanted to acknowledge all of our members in our Education and Training Workgroup, and if I've left anybody off this slide, I apologize. Next slide.

So, in terms of our two questions, we concentrated mostly on the first question; What range of issues related to education should the advisory committee consider when a condition is added to the RUSP? Next slide.

And these were the types of topics that we came up with in our discussions, and it was really a very, very fruitful discussion. So, we started off thinking about what are we trying to achieve or improve in terms of screening through our informational efforts? What do we mean when we say education? Is this awareness, training, should it be directed towards parents, providers, or other stakeholders? Are there increased risks in screening for certain populations? What does

the diagnostic and treatment process look like? Do we have a roadmap? How do parents and providers navigate this? What are some of the aspects of providing support to parents upon notification of an abnormal newborn screen? What types of tools and in what languages are needed so we can appropriately educate different stakeholders?

So, there are many different learners involved throughout the newborn screening system, but we do not want to reinvent the wheel. We discussed an existing tool, what stakeholders need to know, and this was a grid that was constructed, and it's actually posted on the advisory committee website on 2018. So, considerable work went into this tool, and it brings together 31 different stakeholders, and that's matched with what they need to know in 28 categories of knowledge, which is specified for each stakeholder, and at the end of the slideshow, I'll show you an example of that. But it's -- it's really quiet a useful tool, and it was good that we revisited this and

brought this back into the forefront.

So, along the lines of education, there are excellent sources of educational materials that already exist -- the resources in Baby's First Test. There are broader organizations that are putting information together for screening conditions and bringing that into the public sphere. But to answer this question, we need a better foundation to begin with, not just focus on disease-specific information.

So, we discussed considering early education in the nomination process. This can be a bidirectional dialogue to increase awareness across different stakeholders. Early dialogue between stakeholders from the nomination point to implementation can really aid in getting the word out in terms of what people can expect. Getting a perspective on education that's needed early in the nomination phase rather than waiting until a disorder is implemented could really be useful. What role can the advisory committee play within its framework and limited resources? What is the

advisory committee set up to do?

One suggestion was that in lieu of reading the entire report when a condition is nominated or added after the Secretary approves, there could be a one-page description of why this disorder was added and what happens next. The goal of education by the advisory committee could be to tell what is being done as a particular condition is added to it at a particular time breaking down the information about the nomination. This might help improve public understanding as parents and providers may not be aware of the process. People do not often times know when a particular disorder is chosen. Explaining this may give perspective to those who are asking the questions as well as those who are posing the questions.

An example of this in the group was that there's a website in the UK where all conditions are considered -- that were ever considered for newborn screening are listed, and you can click on the condition that did not go forward and learn

why. It seems to aid in helping people understand the general process.

So, can we consider creating something new that will capture important facets of the questions that are being asked? For example, how long would it take in a particular state for a screen for a new disorder to be implemented? Why was a disorder decided upon? What are other states doing? Why is it taking so long, for example, to have a disorder come to a particular state?

Education during decisions about a condition for the RUSP. When is education considered during the decision-making process for a condition nominated for the RUSP, or does this figure at all in the process? The group thought that this was not considered very much as far as we know, but it's an excellent point and it may be captured in the APHL survey of the states or not. But this is an excellent suggestion that came forward.

The group discussed benefits and harms.

There is no agreement among stakeholders for what constitutes benefits and harms in different newborn screening conditions, so this is diverse opinions. One group may feel preventing mortality may be sufficient, but for another, this is not sufficient benefit to consider screening. Advocates have differing views, as do states, and even within the advisory committee itself. There are different thresholds for benefit and screening.

How can we define physical versus psychosocial harms and benefits and the magnitude of each? Potential harms in newborn screening have been present since the very beginning of the screening system. How do we education about potential harms? Is there a way to communicate this within the nomination process? Should it be requested of a nominating group, for example, that they consider benefits and also harms of screening from their perspectives? This is a very difficult topic and defining harms can be challenging for all of us, but it certainly is warranted at

inspection.

Variety of -- different varieties of state screening systems. There is a wide variety of state screening systems, and some take the federal recommendations as is, some have their own RUSP process or decision-making mechanisms. There is a federal layer and then there is a state layer of policy. There are issues considered important to states but maybe less important to the advisory committee. We debated that it could be important to educate the public of these existing differences between states, that not all states were exactly the same and there are differences in approach to screening and available resources.

Of note, there are limited resources in states for screening as well, and costs are not discussed as a rule as an education point. This is especially important now since COVID has seized health departments and new disorders may not be added.

Start with those who are least informed. If we are thinking of a one-page sheet for

education about advisory committee activities, such concerns regarding benefits and harms or differences in state screening systems and panels exist but who should we target? Do we want to make a professional sheet and a nonprofessional single sheet? It was suggested that at least information -- that the least informed stakeholders might benefit the most. Educating newborn screening staff was suggested because not everyone gets to the advisory committee meetings or perhaps policy-makers and health care providers may be the least informed. Perhaps legislators because they are often involved in these decisions at a state level. State advisory committees, because they make these decisions, may not know all aspects of newborn screening.

What types of information? So, for our second question, what types of information and resources would be most helpful when a condition is added to the RUSP? So, there were a few thoughts on this. And the education issue might be useful as conditions as added to the RUSP.

Information could be made available on a variety of targeted conditions such as the identification of late-onset disorders or secondary conditions. What about case definition? What are we screening for versus what we might pick up, and conversely, what might we miss?

Education could help mitigate some of the harm and support families through the process, and education may closely be tied to the nomination and evaluation process, and we can examine barriers to that process.

The group discussed the communication guide during the review process. This, again, was a tool that was created and posted to the website in 2018. So, this is for disorders to help think about how initial notifications of newborn screening can occur and guide the discussion about the conditions.

So, to summarize, the committee focused on education about the advisory committee and the nomination review processes, acknowledging differences in the many stakeholders and state

systems, avoiding reinventing the wheel, and revisiting stakeholders grid and communication guide resources, the topics of harms and benefits, cost, early education in the nomination process, informing the public providers about the nomination process, and informing the least informed among them, and the possibility of creating one-page informational guides or answers to address the questions posed to the Education and Training Committee. Can you just turn to the next slide or the last slide?

And this is just an example of the tools that I have talked about -- the communication guide and the grid.

CYNTHIA POWELL: Thank you, Dr. DeLuca. As you said, there was a lot of discussion yesterday during that workgroup meeting and certainly building upon the previous work of the Education and Training Workgroup will be very helpful as we move forward with this.

So, as a reminder, we're going to hold questions and comments until all three workgroups

have presented.

Next, we have the Follow-up and Treatment Workgroup chaired by Dr. Jeffrey Brosco and co-chaired by Dr. Christopher Kus. Today, Dr. Brosco will present the workgroup update. Jeff, you're muted.

FOLLOW UP AND TREATMENT WORKGROUP UPDATE

JEFFREY BROSCO: Oh, my apologies. And what I said was brilliant, I'm sorry you guys missed it. It's always interesting to see how much the content of what the different workgroups come up with. Even though we have different charges, it's so similar and I think you will hear that as we go through this.

There is no way we can cover the richness of the discussion in our ten minutes, but I'm lucky in that our panel discussions starting at 11:10 is on the same topic. So, I'm going to spend most of my time reviewing what the Follow-up and Treatment Workgroup has been doing over the years because, as Jane pointed out, we've done so much of this work before. Next slide, please.

So, it's interesting even though we have a new group of folks, there's some turnover, that a lot of the discussion we did yesterday led to many of the same places where we were in 2018 and 2019. And I want to particularly acknowledge Chris Kus for helping organize our very unruly group at times. It was wonderful discussion. Next slide, please.

So, just to remind everyone what our charge is, we are responsible for working on barriers, recommendations, and who is responsible for screening, implementation, short- and long term follow-up, and that includes treatment that are relevant to newborn screening results. Next slide, please.

And just a couple words on what we mean by follow-up and treatment. These are very strange things, but we had discussion where we've been using the work follow-up, and for clinicians, this implies treatment. I'm a pediatrician. If I'm following up a patient, that means I'm going to treat that patient every time I see them. But

for many others, for researchers, they may say well, you know, in five-year follow-up, the survival rate was blank. And so, one of the things we want to make sure is that when we say follow-up, we actually imply treatment and its part of our workgroup name.

The other thing is the word long term. When we looked at this really closely a couple of years ago, we realized this means very different things to different people. For some people, five years -- age 5 is long term follow-up. Most of us would agree, well, that doesn't take into account things like learning disabilities and stuff that happens after that. So, we've been trying to use the word longitudinal, which includes lifespan. So, instead of saying long term, I'm going to try to remember to say longitudinal. Next slide, please.

And what are some examples of longitudinal follow-up? So, there are three main categories, and I'll talk about this more later. But what the researchers are primarily interested

in, did early treatment make a difference? Then, there's the quality improvement/assurant, return on investment, which we talked about a lot yesterday and tends to be the purview of particularly larger organizations. And then perhaps most importantly for families and each of us as clinicians at the bedside is how is that particular child doing. So, we want to know over time. And there's obviously overlap among the three. Next slide, please.

So, what have we done to try to get here? I'm going to -- let's skip this slide for now, because we'll talk about it more later.

Starting in 2006 was sort of the first major publication where Alex Kemper and the workgroup laid out some of the central components of what follow-up should look like over the years, and that included care coordination, evidence-based treatment, and quality improvement, and they said there are certain features that were really important. And you see at least, you know, over a decade ago, they laid out most of what we need to

know. Next slide, please.

And then, Cynthia Hinton and the workgroup at that time followed up, emphasized those central components, and then talked about those different perspectives, and we'll deal with this a little bit this afternoon. Both state and nation, primary care, specialty providers, and families have different views on this, and it's kind of went through and laid that out. Next slide, please.

And then, perhaps, most useful is the work of Cynthia Hinton and that workgroup, which created this framework in 2016. So, go to the next slide, please.

I just want to stay on this for a minute because in some ways, as Jane was saying, things have been laid out in previous workgroups. Well, things have been laid out pretty nicely for us. So, you can see on the left side, there are these outcomes, and they are the major outcomes we all think would be important for any condition. And then they talk about the primary drivers. What

are the ways we get to those outcomes? And then even put in place what could be some of the -- conceptually at least -- what should we measure to know whether we've reached those outcomes. Next slide, please.

So, a couple years ago, our workgroup tried to work on those measures in particular, and Alan Zuckerman and others really helped lead us through this to say well, these quality measures are a crucial part of our health care system nowadays. They are the way we know we're getting where we need to get. There are lots of different kinds of quality measures. We talked a little bit about how this would all fit together. And I'll spend more time on this this afternoon when we talk about long term follow-up in that context.

So, and this as well, we'll talk about this afternoon, this idea of a federated system. The United States health care system is highly fragmented. It's just the nature of the beast. There's no way around it. So, if we wanted to create a way of keeping track of all these

different components, we need to kind of federate different pieces of it. Next slide, please.

So, here are the questions that we were discussing yesterday, which fit in with the work we've been doing really over the last decade.

So, the first one, what kind of longitudinal follow-up information should be considered when a condition is added to the RUSP. Next slide, please.

I almost didn't have to change at all our slide from a couple years ago, and we discussed this yesterday morning as well. So, we would argue that when a condition is considered, we should be thinking about longitudinal follow-up right from the very beginning. And I love the way that Shawn McCandless talked about this relationship that the nominating group sort of proposes some ideas and that begins relationships, not just with HRSA and MCHB, but with state newborn screen labs and so on. It creates an opportunity for us to learn from each other.

And the key components that we all agreed

on yesterday -- and this was the bulk of our time -- was that we want to make that we have some access to treatment -- I'll come back to this later this afternoon -- because there are some really tricky issues about what we mean by equity and how far we can go. But there should be at least some ideas about if we screen for a condition, will children who are identified have a chance of actually getting treatment, because if not, that's a real problem.

A second key idea is what is the best outcome measure? How do we know we've been successful in newborn screening? What really matters? And we think the nominating group is in a good position to participate in that discussion and should say these are the kinds of things that are really important to us as researchers, as clinicians, as family members, as youth and adults who have the condition, and they should have a say in what is the important outcome.

And then lastly, that there should be at least a plan, some idea, a prospect of how we

might collect this data over time. Is it a patient registry? Is it going to be through the approaches we're going to hear later this afternoon from NewSTEPs or others?

Now, we -- it's important to say that we think that this process should not be part of the scoring, you know, we shouldn't say yes, everyone has access, and therefore, it should be on the RUSP or not. But that we should at least begin thinking about longitudinal follow-up from the beginning. This has become -- some groups have a lot more access to resources than others, and we don't want to create a bar that people can't reach just because of resources. Next slide, please.

The second question was about systematic review of conditions on the RUSP and when that should be done and then what information would be important, and here are some of the main ideas that came out of our discussion yesterday.

One is the idea that during evidence review, Alex and his team come up with these models that say here are what we think is going to

happen, here is the ratio of benefits to harms, and maybe we can use that as an organizing system for thinking about conditions five, ten, fifteen, twenty years later, and there's also the value that we get some lessons learned. What did we learn from our modeling and how it actually played out?

The equity, population health issues came up a fair amount yesterday in our workgroup. Did everyone benefit from newborn screening state programs equally, or were there disparities that we need to address?

Following up on Mei Baker's comments yesterday, a number of folks talked about well, what actually is the condition? What's that range of diseases once we start doing newborn screening? We have secondary targets, late onset, what's the real prevalence? And that's information that's going to be really important for informing decisions in the future.

And I think you heard Bob Ostrander yesterday talk about harms as a way to prioritize.

What are the red flags and maybe one way to think about when we should review a condition is if the ratio of benefit to harms changes, maybe it's time to do a closer review?

And then Jed Miller had a really nice idea talking about barriers and systematically collecting information in these common categories so states could learn from each other over time.

And then lastly about this, what conditions to review and when. Should it be three, five, ten years? One idea is that it could be sort of a two-step process, and maybe there is a routine where, you know, ten conditions are reviewed every year in a very brief way. So, what does the published data say, a quick survey, and identifying ones there the ratio of benefit to harm has changed significantly and therefore requires a much more close look. Next slide, please.

The third question for us was the cost of treatment, and everyone agreed that this should be something we need to look more closely at, but

there was a lot of feeling that this probably should not influence whether something is put on the RUSP or not, and Annamarie Saarinen made a really critical point, which we all rapidly agreed with, which is it's probably not right to think about this as cost of treatment. You know, if you say something costs, you know, $700,000 a year to implement, that's out of context. And really, what we should probably be thinking about is access, and she suggested the WHO definition, which here -- we'll talk about this a little bit later this afternoon when we talk more about equity. So, we think that cost is worth thinking about, but we really just began our conversation yesterday. Next slide, please.

So, this is just a little hint of what we are going to talk about later in terms of cost and access and equity. And that is, if you think about newborn screening programs at the state level, we do a really good job probably regarding diagnosis in terms of equity, but probably not so much in treatment. And so, that's really one of

the bigger issues we'll talk about as well later this afternoon. We only briefly touched on it yesterday, but these are things we think we can be focusing on more in the future.

And I think that's my last slide, and I will turn it over to Kellie.

CYNTHIA POWELL: Thank you, Dr. Brosco. I look forward to your presentation this afternoon -- you and the others. Certainly, this is such an important area, as you know, one that I'm very interested in and think and hope we can move forward. So many other countries do a much better job than we do in terms of the longitudinal follow-up tracking. So, thank you.

And now, I will turn it over to Dr. Kellie Kelm, who is chair of the Laboratory Standards and Procedures Workgroup and will give us their update.

LABORATORY STANDARDS AND PROCEDURES WORKGROUP UPDATE

KELLIE KELM: Good morning and thank you. Yes, we had a fantastic discussion yesterday. It

was great to see everybody again. It feels like it's been forever, and I want to thank Susan for also obviously helping out. Next slide, or do I do it? No.

So, here are the workgroup members. We had some new members join us, which was fantastic. So, we had Shawn McCandless, committee member, had been hanging out for a few meetings and decided to officially join us. So, we want to welcome Dr. McCandless. And we had two other new members as well. So, it was fantastic to have them and everybody. It was well attended yesterday. Next slide.

So, our question, you know, obviously some of them the same as the other groups, and obviously, our targets were more along the perspective of our participants being people involved both in the public health labs and systems.

So, what information would be most helpful from newborn screening laboratories related to the review of conditions on the RUSP,

and how can we prepare newborn screening labs to collect and report this data? And I also want to say that obviously we had people in our group, not just from the labs, involved in the whole system, and a lot of that is, you know, informed our feedback.

And you'll see that some of this actually does overlap with some of the other groups but, you know, our first bullet was, you know, the fact that we should, as we're looking at -- especially if we're looking at conditions already on the RUSP, you know, we should look at how, you know, how well we are screening for each condition. And so, there was discussion about actually having some objective performance metrics, you know, what -- what would we hope we would be achieving in terms of performance metrics when we're screening for these conditions?

So, you know, sort of having an idea about expected positive predicted value and negative predicted value and I can't say that this would be the same for every condition, but maybe

it should be. States could then look at their own systems and determine whether or not they're meeting the NRP and PPV for that condition.

We should also be looking at evaluating and reporting the false positive rate and false negative rate. Obviously, you know, many of the conditions already include a second-tier test, but some of this information, you know, has probably already been used for many programs to determine the use of second-tier tests, but it may also be a great way to look at some of the ones that are already on the RUSP.

As defined and stated by some of the, you know, the two preceding groups, you know, we must start with a good case -- a good case definition. You know, you can't calculate what's in the first -- the first bullet without actually stating that this is what we're doing these calculations for.

So, then obviously we can look at what each state is screening for and what else that they're finding. You know, I think that, you know, that this does differ by state, obviously,

based on what they may also define as, you know, both case and what they're screening for, but important information to consider as you're evaluating your objective performance metrics.

You know, we also have to acknowledge that case definition could change over time and has for some of the conditions. So, you know, we would have to figure out some way to sort of, you know, revisit that as we go back and look at conditions on the RUSP.

In terms of collecting and reporting data, everybody in the committee pointed to NewSTEPs being available and a place that we can use to collect the data since, you know, data is already being funneled into that -- into that resource. Obviously, the difficulty for everybody always is that there, you know, they are not interoperable with NewSTEPs. Obviously, there is always that data processing and input step that must occur, and obviously, you know, it is sort of a time-limiting step sometimes.

And it's funny, we did -- although it's

been a while -- I do remember that former committee members, Dr. Rinaldo and Dr. Mettern, had actually presented to the committee -- I forget how many years ago -- they published their own evaluation of mass spec-based screening and had actually suggested some metrics to evaluate screening, which I believe was PPV and false positive rates and detection rates, excuse me. So, it's something that had actually been previously proposed by other members of the committee. So, I just wanted to mention that. Next slide.

The second question is should there be more in-depth information regarding cost to labs for adding a new condition to the panel or is there already enough information provided? So, just remember that as part of each condition, there is a Public Health Impact Assessment, you know, there is an information -- survey going out -- more detailed survey to programs that are already screening for that condition to get more detailed information, and a readiness tool in

order to try to get information on, you know, will your program need new instruments, employees, reagents, et cetera.

You know, I think the feedback I got universally from everybody is that, you know, although some of this information has been helpful, we're still not getting the cost of the overall system, and I didn't put it here, but I think a lot of people have, you know, seen Susan's diagram -- she had it yesterday in her presentation -- that there is still a lot that we're not capturing in our assessment of the cost and that we shouldn't, obviously, just limit it to labs but the whole system.

One suggestion, you know, obviously we have -- the survey is limited. You get some information, get some readiness, and then get more detailed information, as I said, from labs already doing it. But, you know, we have labs, you know, and the survey goes across all groups. But you're going to have some labs that are going to be more ready than others and it might be really useful to

use more of a what we call bucket approach, you know, with presenting and breaking down the cost to the system by states that are starting at different levels of readiness. You know, and I think back to like when we brought on SCID and the idea about adding molecular testing, you know. Some states were much more ready than others, and it might be really informative to the committee if we actually were able to look at what, you know, the difference might be in terms of time and cost if we sort of, you know, consider that and stratify by different levels of readiness.

But I definitely think we're just hoping for -- although we also acknowledge that it's hard, it's not easy, that we need a more, you know, the estimate of the cost needs to involve more than it is right now. Next slide.

Are there any other considerations for enhancing either the nomination process or review of conditions on the RUSP? You know, and unfortunately, we didn't have as much time to talk about this one once we got through the other two

and have some overall, you know, I think one of the things that we heard was they really thought that both for our committee discussion as well as something that really helps state programs is when we have a better definition of the condition under review for the committee as well as the states going forward, and the example was the SMA definition because it was actually described as what we were looking for.

I think the comments that I received and wanted to pass along was that, you know, the information that we've been getting from, you know, as part of the evidence review process has been extensive and very thorough and that the feeling was that it will benefit from those enhancements that Alex talked about yesterday. So, you know, we didn't have much else besides obviously even talking about the cost on the previous page about, you know, information about the evidence review, for example.

Something that just kept coming up and I think that, you know, we were talking about -- we

wound up getting on the topic about reviewing conditions on the RUSP and the process of potentially, you know, reviewing and removing, you know, because I think that's something that people are interested in that discussion and obviously some of them have also had these discussions in their own programs. And a lot of people thought that, you know, one of the interesting things that they've noticed is confusion about what the RUSP is. Many interpret that the intended screen is for both primary and the secondary targets on the list; however, you know, the RUSP is the list for primary targets and obviously, the secondary targets are ones that are often also screened for in that process.

So, there are those that have the RUSP or the requirements that screen for the RUSP in state law that is then interpreted to screen for primary and secondary targets. You know, the discussion was that for some programs, that has been, you know, they have actually been able to talk to their programs about removing some secondary

targets from their screening program and SCAD was given as an example and, you know, sort of educating the people in their state and their clinicians and their programs that, you know, they had the flexibility for the secondary targets.

So, you know, we had several suggestions, people were very interested in this, and some of the suggestions were education for everyone in the system -- so, this is states and clinicians -- about the secondary targets. And one person had some pointed suggestions for the wording and display of the RUSP on the committee website, feeling that it added to the confusion. But this was just interesting discussion about some states already taking on some of their own initiative to review secondary targets and remove them from the state program. So, you know, that came up multiple times.

So, I think that that's it for us. As I said, it was -- it was a very fruitful and enjoyable discussion and thank you very much.

CYNTHIA POWELL: Thank you, Dr. Kelm.

I think one clarification, and this was something that I had asked about, you know, as we talked about reviewing conditions already on the RUSP. The committee would be considering both the primary and secondary targets as we go through this process. So, I think, you know, your workgroup suggestions are very helpful as we think about how things are presented on the website and confusion about that because I think a lot of people do have confusion.

DISCUSSION: WORKGROUP IDEAS

All right. So, we heard some very interesting ideas discussed by the workgroups. I will now open the floor for discussion. Committee members will discuss first followed by organizational representatives. As a reminder, please use the raise hand feature in Zoom when wanting to make comments or ask questions. When speaking, please remember to unmute yourself and state your first and last name each time you ask a question or provide comments to ensure proper recording. Okay, sorry, let me just get my list

here so I can see. All right, Jeff Brosco.

JEFF BROSCO: Thank you. Jeff Brosco, committee member. So, Kellie, I want to come back to something you said about the cost estimates and how difficult things can be to gather. And I'd like to maybe separate out information that we gather from that nine-month period that allows us to make a decision about adding to the RUSP and information that might come afterwards. And I'm actually going to say something nice about Scott Shone -- don't hold me to this -- but one of the things we did in Florida when we got to that point where we decided, yes, we think, you know, SMA, for example, had been added to the RUSP, it was very useful to get a state-specific estimate of what it would actually cost -- and not just cost in terms of financial, but also how many neurologists do we have and what access do we have to this and that, and what would it really take for the Florida lab to be able to get up to speed. And it was really helpful for things like how much money should the state legislature budget in order

to add SMA? So, even things that may or may not be sort of specific to the RUSP and whether it's added or not, a lot of information post-RUSP might be really useful as states are trying to actually implement. Anyway, I said something nice about Scott for a change. There you go.

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Hi, everybody. Very interesting. I listened to the workgroup reports. I did pick up one recurrent theme as we talk about RUSP conditions and Dr. Powell also emphasized that. I think with everything we need; I think it goes to the fundamental thing, which really is when we nominate a condition -- when we're put it on the RUSP, what's our intention? The condition we intended to screen for and many people, you know, I think every workgroup mentioned what are we screening for and what are we also picking up? I think if we do the review, I think to me, there's a more fundamental thing. I hear so many people have an interest and knowing we have a concern that exists. I am wondering if the chair

of the committee can think about having a workgroup, you know, the laboratory standard group and also maybe education group somehow, some way, since magically to review that. I think RUSP has been used for quite a while now and I think it has been benefitting in so many, many ways, and on the other hand, what's the [indiscernible 47:17]? Do we need to more state clearly and educate people really was about? I think [indiscernible] and I do believe like SCID and SMA really gave us the way to think about things, like the marker -- what do markers give to you and leading the condition that you can kind of [indiscernible 47:41] for them.

And I think about the tandem mass assay as if you think about the condition, then think about the action sheet. Actually, the action [indiscernible] they did, I mean, they do state other markers. So, I think if we do have some material and the baseline, we can do a little bit more systemic review and sometimes we can update our website how can we define, and I think it will

be useful. Thank you.

CYNTHIA POWELL: Thank you. Scott Shone.

SCOTT SHONE: So, first of all, thanks to Jeff for saying something kind. I appreciate it. But I will say that -- that work with the Florida Advisory Committee, I think it's another example of what I was talking about yesterday on the cranes and the freight train, right? So, to go back to that metaphor is that Florida has an understanding -- has the law about having to onboard conditions but their advisory committee is that final -- final arbiter and wanted a robust evaluation specific to their state taking lessons from the RUSP but also any states that have been implemented.

And so, I think that -- so, they hired a group to come in and evaluate their state and provide that overall system impact for Florida. And so, it takes sort of APHL's national look at the PHSI and brings it more local, and I think there's an opportunity and we always say that if you've been to one state newborn screening

program, you've been to one state newborn screening program. But I do think that we do in general have buckets. So, there's not fifty solutions. There's not one solution. There's something in between. So, I think there's a lot to gain.

Maybe HRSA, we can think about -- the committee can think about working with HRSA on a program to help sort of bucket out, as Kellie was saying, around where states are so there's a better gauge as opposed to the broad whole national view, but based on resources, you know, coming from Jersey reflecting on how resource rich we were with our metabolic geneticist and our endocrinologist and their pulmonologist compared to other states. I think there is a real need to assess that and evaluate that when we're looking at these impacts.

And so just [indiscernible 50:08], I think that programs need that that crane to help do that assessment for them as they bring our conditions.

CYNTHIA POWELL: Thank you. Robert Ostrander.

ROBERT OSTRANDER: Sorry, had to unmute. Robert Ostrander, AAFP, org rep. I've got two comments on the subjects we talked about. One is just to fill out Jeff's amazing brief summary of our work yesterday, when you -- one of the slides said one of the things we should measure are the patient care realm of longitudinal follow-up is the patient getting care in the appropriate setting.

One of the things that I think is important at the nomination level is not are they getting care or is there capacity because we're not going to know that, but what does the vision of longitudinal follow-up care look like. It seems -- it's my experience with -- I'm on the advisory committee over the years -- when we look at a condition, we have a pretty good picture of what is going to be done if the condition gets added and implemented for those children in the first few months when the intervention is done and

we're starting to get a sense for the conditions for the delayed onset form how a surveillance might happen. But I don't always think we have a very good picture of what the -- again, this is going to be a vision because it won't have evolved because the condition hasn't been around long enough -- but through the pilot studies, there will be some kids that are out there. What is care doing to look like at the 2-year mark and at the 5-year mark, and not so much is the kid getting the care, but at the time of nomination, what do we imagine that might look like? Do we imagine it might look like -- again, you know, my bias always is a combination of medical home and specialty center, but you know, a little more specifics to the condition? So, I would like to see part of the nomination application and not a thumbs up or thumbs down, part of the nomination package to indicate that there's been some thought given into that once we treat these children, what will their care look like 2 or 5 years down the road.

And then, the other issue is this, you know, concept that we need to look at harms on the review side when conditions are brought back up because that ratio may change because of all the milder cases that get detected once we do universal screening, et cetera, et cetera.

And all I wanted to point out is the suggestion to the committee that as we look at this, that we get some input from USPSTF folks, and I know Alex sat on that for quite a while, Alex Kemper did, because they're -- they've got a system in place and they're pretty expert at looking at their public health recommendations periodically and then doing revisions, and a lot of that has to do with harm/benefit reviews and sort of putting the different harms and different boxes from the economic to the psychosocial to the actual medical harms versus the benefits, and it's something we have struggled about in our workgroup yesterday was there's all these different kinds of harm, and how are we going to do this, and I just want to suggest to the committee if we do decide

to do something with this, the committee tap Alex and the USPSTF and learn about their process, because this is something they've been doing for years, and it's very much analogous as a public health recommendation that once it gets done, new information arises. Thank you.

CYNTHIA POWELL: Thank you. Very good suggestion.

Debra Freedenberg.

DEBRA FREEDENBERG: Hi, good morning. I just wanted to expand a little bit on the previous comments in terms of what we think about with follow-up for these conditions. One of the things I just wanted to expand about is that when we talk about milder conditions and think about what the implications are, many of what we call "milder conditions" have a significant impact for that particular child's medical care and morbidity and hopefully not mortality with them, but something we're calling mild really does require a lot of medical intervention, and it requires care as well. And I'd like us to keep in mind that the

spectrum of disease that we clinically classify as mild may not be mild for the medical care that family and that child as well, and so, just when we think about the spectrum.

And I also do really agree that we need to think -- when we think about long term follow-up, we, you know, talking through the lifespan, we do need to think about a system-wide approach rather than just the newborn screening program approach, and I think that's been really evident in everything that's been presented and said and would like to continue to think about as new conditions are being proposed, we start or in more depth start to think about what the system-wide approach would look like and not just a programmatic approach.

CYNTHIA POWELL: Deb, I hate to put you on the spot, but could you give us an example, you know, I'm sure you have some in mind when you're talking about, you know, milder conditions that really have a significant impact on that child's medical care.

DEBRA FREEDENBERG: Well, I mean, you take MPS1, you know, some of its mild, some of its not, and some of its requiring significant treatment with that. For CAH, we know there's an ongoing discussion about what nonclassical CAH looks like and the impact and treatment that's needed in childhood, maybe not affecting neonatally, but that continues to be needed. And if just go back to XALD, we consider the mild variants, you know, those that have onset later on, but it impacts their life and their, you know, their quality of life as well as the medical care that's needed if you're going to become -- because of your motor issues become wheelchair-bound or whatever. I mean, those are all significant medical issues, and so, you know, in the diagnostic odysseys that people go through. So, those are just some things off the top of my head. But, you know, as we all know in the metabolic, they're also, you know, we can consider something mild and yet the child can be in the ICU being resuscitated from a metabolic decomposition with

something we call "mild" like cobalamine C or something like that, and I know that's a secondary. But, you know, we say it's mild, but it can present and be as life-threatening as some of the other conditions as well.

CYNTHIA POWELL: Um-hum, thanks. Annamarie Saarinen.

ANNAMARIE SAARINEN: Hi. Thank you, Annamarie Saarinen, committee member. I appreciate what Deb just said. I was kind of leaning into that a little bit in my comments. And again, I have a little bit of a lens with CCHD and knowing that it's the outlier and it just has different considerations. But that said, I think a lot of what -- what you were just saying, Deb, is true for both of the point of care screenings that are non-bloodspot at this point and how we would look at maybe things like that that could come up in the future, right?

So, a lot of these kids would require monitoring over time. There's a huge variation between a baby that's going to need to undergo

cardiothoracic surgery in the first few days after being picked up by a newborn screening program and a baby that has maybe till falls into the CCHD or the serious congenital heart disease category that just needs to be coming in every two weeks, every four weeks for evaluation and may not need surgery until their 4 months old or 6 months old. Either way, it's still critically important, and it leads into sort of that other piece of what Dr. Kelm was talking about on secondary conditions, and I know we've had this discussion before, and I think Mei Baker has some very articulate perspectives on this. But -- well, actually a lot of people in this group have articulate perspectives on this. But the secondary conditions -- the ongoing sort of lack of clarity of how they fit into our evaluative and our framework for data collection and tracking is -- is still -- it's a little bit of a point of frustration, and I don't know if it's because we -- it's just too hard to tackle that within, you know, one of the -- one of the workgroups to advance what would be a really -- a

more formal recommendation of how the committee thinks about that and how it thinks about it not just when we look at the conditions, but after the conditions are already on the panel.

But I think we all realize that just the definitions of what those secondary conditions are and how we're categorizing things from false positives to true positives for a non-target condition or a secondary condition is -- to me, it's just so mission-critical to a public health program. If you -- if we don't get this right, how do we report out to the rest of the world, wherever they may be, that we've been successful or moderately successful or a failure because all of those things could be true, under which different folks interpret how to report on what's a positive screen or what's a false positive screen or what's a true positive for a secondary condition.

So, thanks for letting me share that and for all the hard work that all three of the workgroups have done here.

CYNTHIA POWELL: That's really a key point.

Jennifer Kwon.

JENNIFER KWON: So, I -- well, I think -- I'm always kind of curious when people talk about harms and reviewing programmatic responsibilities and scope, like sort of the specifics they have in mind, because like everyone else, I think I'm sort of driven into making comments based on my specific experience, and I think that that gets difficult. And one of the things it reminds me of is that I wonder what -- I wonder if we could come to some consensus about what the scope of responsibility of the advisory committee's activities would be.

So, it was interesting listening to Kellie's talk about sort of the laboratory perspective because, of course, that's where newborn screening starts. That's where we think of the home of the public health enterprise, data collection, and screening, and reporting out the results. And then, it gets into the education

phase, and then that's where we know that there are some breakdowns in terms of how people understand the information they're being given, and when I say people, I mean providers and patients and their families in terms of what constitutes a positive screen, how to react to it, how to implement treatment.

And then, I think, the Long term Follow-up and Treatment Group has such laudable ambitions, we want to implement early care knowing that many of the programs result in us not really implementing early treatment. The early care doesn't necessarily involve an initial treatment. It involves early initiation of surveillance that can have considerable impact on families, as I think Deb was alluding to -- Debra Freedenberg was alluding to. But not necessarily like necessarily actionable results like, I think for families and providers, it can feel very frustrating getting into this cycle of surveillance.

And so, when we review these programs -- and I think it would be worthwhile reviewing them

-- I think we also need to keep in mind just how messy it gets, and I think that some of what we're looking at in terms of long term follow-up and treatment perhaps needs to really be in the realm of specific specialists and specific groups and advocacy groups. And so, I think for me, it's more just trying to frame how we are going to go about looking at these various disorders and deciding on how effective or how successful we've been.

CYNTHIA POWELL: Thank you. Thank you, once again, to all the workgroups for your very valuable feedback, it's much appreciated, and to all of you who participated in this discussion.

We'll now take a break since we're a little bit over. Let's say 11:15, we will reconvene eastern standard time -- reconvene at 11: 15. Thank you.

BREAK

CYNTHIA POWELL: Welcome back, everyone. If I could just ask the committee members if you've rejoined if you could start your video.

That way we won't have to do the full roll call again, but we'll know that you're present. Thank you.

For our last session of this meeting, I'm pleased to welcome a panel of four presenters who will discuss innovations in long term follow-up. Dr. Jeffrey Brosco will set the stage in his discussion of long term follow-up as a key component of ensuring the best possible health outcomes for children and families identified through newborn screening. Dr. Brosco completed an M.D. and a Ph.D. in the History of Medicine at the University of Pennsylvania. He served as chief resident after training in pediatrics at the University of Miami, Jackson Memorial Hospital, and he is board-certified in pediatrics and in developmental behavioral pediatrics. Dr. Brosco serves as chair of the Pediatric Bioethics Committee at Jackson Memorial Hospital and associate director of the Mailman's Center for Child Development.

Dr. Brosco has had a series of leadership

roles in the Florida Department of Health including serving as the deputy secretary for Children's Medical Services from 2016 to 2018. He is now Florida's Title V Children and Youth with Special Health Care Needs Director.

Following Dr. Brosco, we'll hear from Carol Johnson, who will provide an overview of APHL's Long term Follow up Taskforces, Long term Follow up Landscape Survey. Carol Johnson has been the Iowa Newborn Screening Follow-up Coordinator since 2011. The program also screens and provides follow-up for three other states: Alaska, North Dakota, and South Dakota. She coordinates the Quad State Initiative and sits on the Newborn Screening Advisory Committees for Alaska and North Dakota. Ms. Johnson has co-chaired the APHL Short term Follow-up Workgroup since it was developed. She is also the co-chair of the APHL Workforce Taskforce Workgroup since its beginning in 2019.

We will then hear from Dr. Mary Schroth, who will discuss long term follow-up for

individuals identified with spinal muscular atrophy. Dr. Schroth is the chief medical officer at Cure SMA, where she leads the SMA Care Center Network and SMA Clinical Data Registry to collect real-world evidence about care and treatments for people living with SMA. She also advocates for the implementation of SMA newborn screening with state public health labs and officials and health care professionals across the US. Dr. Schroth is Professor Emeritus of Pediatric Pulmonology at the University of Wisconsin, School of Medicine and Public Health, where she provided care to children with neuromuscular disorders for twenty-five years.

Finally, we'll hear from Dr. Amy Brower, who is a medical geneticist at the American College of Medical Genetics and Genomics in Bethesda, Maryland, and is the co-principle investigator of the Newborn Screening Research Network.

Dr. Brower directs a team that develops informatics platforms, resources, and tools to

collect, analyze, visualize, and share longitudinal, clinical, and genomic research data to better understand genetic disease across the lifespan. She has a background in medical genetics, genomics, informatics, FDA submissions, newborn screening, translational research, molecular diagnostics, and bioinformatics. She was a member of the Human Genome Project and International HapMap Project and developed molecular diagnostic and informatics platforms over a decade of work in the device industry.

Dr. Brower was an inaugural member of this committee. She is the parent of a son with severe combined immunodeficiency.

Next, I will turn it over to Dr. Brosco.

INNOVATIONS IN LONG TERM FOLLOW-UP

JEFF BROSCO: Thank you very much, Dr. Powell. My job for the next fifteen minutes or so is to try to sum up a lot of what we talked about yesterday in the context of nominating new conditions and then a bit about what our workgroup has been working in, which you heard just an hour

or so ago. And I'll make a couple of comments on specific items that are really important for us to look at and then set the stage for the rest of the panelists. Next slide, please.

So, just a reminder that this, I mean, this topic is such an important one, and we've had a workgroup working on this for well over a decade, and I won't go through all the details of this because you heard me say all of this at 10:15 this morning. But just remember that our workgroup is charged with looking at barriers, recommendations, and responsibility, and really, we've been most interested in longitudinal follow-up over the last decade because that's where a lot of the action is. And just a reminder about language -- I'm using follow-up to include treatment and imply treatment, and we're trying to use longitudinal rather than long term because it seems to be more Catholic.

And then, you see just those publications that we've been working on in the Treatment and Follow-up Workgroup to make sure that we are

following that sort of pattern of setting out what the broad ideas are and then looking more and more closely and getting down to specific quality measures. Next slide, please.

And this is the framework I just showed you an hour or so ago. It really lays out neatly all of the things that we need to consider in any kind of network system that looks at longitudinal follow-up. Next slide, please.

I do want to emphasize a couple of these points, although you probably heard me say them yesterday morning and this morning that this idea of access to treatment -- I'm going to come back to it in a few minutes, so equity and where those potential barriers are -- is really an essential one and we see this play out both in national and state level as we're trying to decide what to add to the newborn screening programs.

We've talked enough, I think, about outcome measures and population-level data, but we'll touch on a few of those as we talk about how we might actually implement that. Next slide,

please.

So, I just want to dig into this federated system idea a little bit. And again, we start with the premise that look, the United States of America has a very -- what's the right word -- variegated approach to health care systems. In some ways, newborn screening is an anomaly. It's one of the very few things where we try to set national standards and states implement it, and that's really remarkable for medical practice and health care practice. We don't have, you know, we're done Denmark or Sweden where we have national datasets where we can keep track of folks. So, it makes it really hard. So, this idea that the different players could work together and create this federated system so that every child identified with a newborn screening condition gets high-quality, evidence-based, family-centered is kind of our goal.

So, there's different ways of thinking about this, and I'm not going to say too much now because in some ways, this is what the rest of the

panelists will talk a lot about. So, whether it's the LPDR that NBSTRN has put together, we'll hear more from NewSTEPs program from APHL, Cure SMA obviously, and there are other systems and models out there. NIH has its Rare Disease Clinical Research Network and Region 4, for a long time, has been sort of following up on Errors of Metabolism. So, there are systems out there to work within the newborn screening world that we could tap into.

And obviously, the electronic health record and artificial intelligence are moving forward in fits and starts and this is a way that we could create a more interconnected information system that can answer a lot of questions. Obviously, we're not there yet. We're frustrated by a lot of this, but it's possible. With enough financial resources, anything is possible. We are looking at -- our workgroup has talked about certain kinds of federal and state partnerships to make that happen.

I'm going to talk more about equity in a

second, but I do want to say this idea of defining who is responsible at each stage -- this roadmap idea -- if you could go to the next slide -- just too kind of give you a sense of the players.

The first thing to keep in mind is why do we need a federated system -- because there are differing goals, and I mentioned this this morning. Some people are most interested in the research part. We want to know, did something work, is early identification through newborn screening, does it truly lead to improved outcomes or if we just discovered most of these kids clinically, would it have been about the same. What else can we learn from changing the natural history of a condition by newborn screening? So, lots of research questions.

The idea of quality improvement and assurance happens at a lot of different levels, and I'll talk about the players in a second. But one just simple question is, you know, did this child -- we identified him -- did he or she get treatment, and what was the outcome, and it could

be very simple things like yes, they got treatment and they are still alive at age 5 and they do not require special education at age 10. It could be simple kinds of data points like that.

And then the idea of what's the impact of the newborn screening program on a condition, you know, we implemented newborn screening. What kind of impact did it have at a broad level? Can we see that there are decreases in the number of children who have long term effects of newborn screening conditions? And then, the most obvious for most of us is the clinical care. So, how is this particular child doing? Is he or she getting what they need and how -- what's their long term prognosis? Next slide, please.

Then, if you think about the different players, there are different groups that have interest in this group of children, and it's helpful, I think, to see the newborn screening population as part of the larger subset of Children and Youth with Special Health Care Needs, which is, of course, part of the larger group of

all children.

So, if you look at -- there are 4 million children per year born in the United States, there's 80 million children or so -- children with special health care needs constitute about 15 to 20 percent of those children -- depending on how you define it -- and that's any child who has greater than usual need for medical, social, educational intervention, and newborn screening conditions are kind of a subset of that and probably around maybe 1 or 2 percent of kids, depending again on how much you include in the newborn screening.

And so, different interest groups might be interested in different groups of children. So, Maternal and Child Health Bureau, Medicaid, State Departments of Health, we are worried about all children and we want to make sure every child gets the care that they need.

The State Title V Programs, Children with Special Health Care Needs Programs -- we're particularly interested in that second sort of

circle of 20 percent of children that have a special health care need. Newborn screening programs are obviously kids who have a diagnosis in the newborn screening program.

Clinicians, researchers, family members tend to be focused on that particular child in front of them. Of course, many feel much greater responsibility to the larger population of children with newborn screening conditions. Next slide, please.

So, when you put that together, you know, you say well, what's the role of the -- of the advisory committee? What are the things that we would be most important? And I mentioned this earlier this morning, our first [inaudible] from the workgroup's point of view is that we could use the predictions -- those predictive models from the evidence review is one way of thinking about the benefits of the ratio of harms and benefits. I'll come back to equity in a minute.

Mei and others have talked a lot about the case definition and the change in how we think

about each disease once we start doing newborn screening. There's been a lot of talk in the last day or two about harms. I'll point out that Aaron Goldenberg has a couple of really good papers on harms that sort of lay out some of the details and ways of thinking about that in categories.

And this idea of barriers, we want to come back to after we hear from the NewSTEPs folks and from LPDR to see how barriers to treatment might fit into the systems in place that are already there. Next slide, please.

All right. So, some of the new stuff now. I mentioned this earlier. If you look at equity in newborn screening, that is one of the true values in terms of diagnosis in newborn screening and a few of us had a paper a couple of years ago that looked at this and Scott Gross was an important part of this. And what we said, for example, if you look at SCID in the years before newborn screening in California, 80 percent of the children who had bone marrow transplant for SCID were white non-Hispanic. In the two to three

years after newborn screening started, it completely reversed. So, 80 percent of children who got treated with bone marrow transplant were either Black or Hispanic. And what we had thought was a genetic disease or white non-Hispanic families turned out to be entirely about access to diagnosis, and it's a really good example among many of how once we have true equity in universal newborn screening that we have a real change in how well populations are doing.

The problem is that although we've done fairly well on the diagnosis side, we have not done so well on the treatment side. And Alex Kemper and Scott [indiscernible 1:31:40] and I recently wrote about this in talking about the many ways that we do not have equity when it comes to things like getting antibiotics for Sickle Cell Disease, getting treatment for hypothyroid or PKU.

In the figure there is one you've probably all seen. Maybe one of the ways to think about it is on the equality side where you see those three square blue boxes at the bottom.

That's kind of where newborn screening programs are in terms of diagnosis. We're really good at that sort of every single child getting the diagnosis from newborn screening. On the right side -- the equity side -- it's probably where we'd like to get for treatment, and that is, could we imagine if the boxes multiplied to make sure that every child reaches that apple -- the apple being treatment. Next slide, please.

So, I mentioned this this morning that when we talk about equity and access to care, we should probably use this broad definition from the WHO. Just to mention -- I know this is a little blurry and I apologize for that -- I did it last minute -- but availability is the idea that whatever we think is necessary, whether it's a medication, a device, or a treatment, is actually physically available to folks. Affordability is sort of obvious that people can afford it. Accessibility is geography is one of the things, but it also could be about disability. Appropriateness is whether it's scientifically

valid and meets a local need. Acceptable to the cultural beliefs. So, you can think about, for example, PKU foods and whether that works for different populations. And quality, is there some that we are keeping track of it.

So, we would like to have a pretty broad idea of thinking about access to care. Next slide, please.

And then, just in the last 12 hours, I had a really interesting E-mail exchange with Annamaria Saarinen and Scott Gross, and it was important enough that I thought it was worth just quoting at length, and they gave me permission to do so because it's a really neat description.

So, this is Annamarie, and she's saying, "Sometimes you can't have everything in place to start," meaning equity. "I think that you used an example," and she's talking about me "about a situation where only half the kids get access to treatment." And just to back up for a second, this was a question about, you know, parents saying well, if only half the kids can get

treatment for SMA, that's worth it because those half children will do well. But she said, "The conditions are," you know, "condition specific." And then she said, "Of course, children should have access to treatment for identified conditions. But access cannot mean exactly the same thing for every baby and family. The family from Fargo has to travel to Minneapolis for their child's treatment and follow-up. The specialist has a very different experience than I do. She goes 12 miles from the University of Minnesota. People lose their livelihoods over this thing. My husband and I have thousands out of pocket in costs to stay in hotels and motels during Eve's heart surgeries. That would be completely impossible for many families. I guess what I'm saying is we can only try to level the playing field. It cannot be excused to delay implementing something that can help a portion of babies until the rest of the investments in infrastructure and more equitable access can happen."

So, right there, I think, is a really

good statement of one position on the equity question, which is we can't wait for a perfect health care system and a perfect world. Sometimes we need to start somewhere and just starting can then spur equity. It's a really, I think, heartfelt and eloquent description of that position. Go to the next slide, please.

And then, Scott weighed in and sort of emphasized what Annamarie was saying about the cost of care being a lot of things, not just medical costs, but transportation, lodging, child care, loss of earnings, and he also points out that systematic things that lower SES is associated with these sort of barriers. There are psychosocial barriers, there is lower health literacy, and then he talks about trust in our health care system and communication differences, and there's no doubt that both implicit and explicit bias are rife in our health care system and reduce access to care, depending on race/ethnicity, language, social class, a whole range of things. And he concludes, as I think a

lot of would agree, that "Disparities in access are unfortunately the norm in this country." Last couple of slides -- next slide, please.

And so, I sort of responded, we can't expect newborn screening programs or researchers or clinicians or families to solve all the problems of the US health care system or issues of racism or inequality. "On the other hand, newborn screening is a public health program. So, I think that implies a greater obligation to meet the treatment needs of infants and children." It's sort of this idea, don't tell me my kid has PKU and that you can't help me with formula and foods. It doesn't really help me if I can't get what I need for my child.

So, while we can't expect to solve all the inequity in the US with newborn screening, we probably need to go a bit further than we do now. So, this is just trying to frame in some ways the real issues in the equity question. It's not as simple as it looks, and it does have some impact on us as we're thinking about how to expand

newborn screening to new conditions if treatment is really not available to every child. Is it okay to go forward if some kids benefit, meaning some kids won't? Next slide, please.

And then, just sort of to conclude and set up for the next group, at least from the workgroup's point of view, we still have the same charge to look at barriers, recommendations, and responsibility and some potential next steps that we can offer to these questions are obviously continuing to work with the advisory committee on the nominating process change that we've been talking about yesterday and we'll keep talking about, and then, really importantly, and this fits in with what the other panelists are going to talk about now is what would that roadmap for a federate system look like? We're not going to have a single electronic health record or data system any time soon, but how could we work together to sort of patch something that works, and that would include thinking about what conditions to include and when, what information

is most relevant to the Secretary's Advisory Committee, and who is responsible for adding that information. And then lastly, sort of following up from those quotes from Annamarie and Scott and me, we need to keep discussing this issue about access and equity. It's obviously a critical social issue, and we need to think how this fits into newborn screening policy and practice. Thank you.

CYNTHIA POWELL: Thank you, Dr. Brosco. We're going to hold questions and comments until all the speakers have gone. So, we will next hear from Carol Johnson.

CAROL JOHNSON: Thank you, Dr. Powell, and thank you to the committee for inviting me to speak with you today.

So, today I'm going to talk about the NewSTEPs Long term Follow-up Taskforce and some of the deliverables that we have been able to accomplish so far, and it does fit very well with what we've been taking about already, and thank you, Dr. Brosco, for setting the stage. Next

slide, please.

So, in May of 2018, back when we could still meet face-to-face, the APHL hosted a National Short Term Follow-up Stakeholder's Meeting for -- to present a forum for follow-up staff to be able to discuss solutions to some of the common issues that we had. During this meeting, the Short term Follow-up Workgroup decided to create five distinct taskforces to address some of the needs in the newborn screening community with the focus on long term follow-up.

We did create a Long term Follow-up Taskforce, and we asked them to address the role and scope of newborn screening programs in long term follow-up to assess the effectiveness of long term follow-up and to justify the implementation of long term follow-up with program administration. Next slide, please.

The next several slides highlight some of the deliverables that we have been able to accomplish so far. Next slide, please.

So, the Long term Follow-up Taskforce

began to meet monthly in January of 2019 and after much discussion -- because this is a complicated situation -- we decided to focus on two projects. One was to develop a working definition of long term follow-up and the other was to assess the long term follow-up landscape across newborn screening programs. We used this working definition to guide us to develop the questions and the data elements for a survey that we sent to newborn screening follow-up programs. Next slide, please.

We called this the Long term Follow-up Landscape Survey. It was 20 questions long. We welcomed responses from multiple entities per state. We distributed this to 76 distinct contacts and 54 distinct states or territories. This survey included newborn screening staff from hearing, CCHD, and dried blood spot screening programs, and ultimately we received 42 responses for a survey completion rate of 55 percent. Of these, 32 of the responses were complete and 10 were partial responses, and we excluded those

partial responses from the data analysis. Next slide, please.

We chose to highlight some of the questions for this committee today. Here is -- one of the questions that we asked was what is the current state of long term follow-up in your state? We had some that said it was fully implanted, partially implemented. Half of those 32 surveyed programs stated that they do at least some long term follow-up activities, while you see there is a 41 percent response rate that they have no plans to implement a long term follow-up program at this time. Next slide, please.

The next question we ask is how are you funding your long term follow-up activities? We had several responses that they used their newborn screening fee. Some are using grant funding. Some are using state funding. Over 50 of the respondents that said that they're using their newborn screening fee also reported it as their only funding source in higher proportions than those who reported that they use grant or state

funding. That was at 38 and 50 percent respectively for the grant and state funding sources. Next slide, please.

Then, the next question may be the most important question, which was, what types of long term follow-up activities are being performed? And you can see here that there were multiple answers, and these are all valid long term follow-up activities, of course. But I wanted to draw your attention to the first three responses. When you talk to follow-up personnel, they'll tell you that well, long term follow-up is this or long term follow-up is that because we still really don't have a true formal definition of long term follow-up yet. And so, many say that it's the data collection from the clinical providers, others will say it's facilitating clinical care follow-up, while others say it's connecting individual families to services and support. Again, all of these activities that you see on the grant are important. And, in fact, 42 percent of our respondents stated that they do actually more

than 4 distinct long term follow-up activities. Next slide, please.

These next two graphs illustrate what percentage of conditions on your newborn screening panel receive services or activities, and you can see there is some differences based on condition, and we're going to talk about that more in a little bit as well. And then, the purple graph shows what percentage of individuals identified through newborn screening have received long term follow-up services or activities, and it's a slightly different response there. Next slide, please.

Then, was asked what you are doing with this data that you're collecting, and several responses said that they used this to track the babies that are lost to follow-up, which is actually one of our quality indicators, that they track clinical outcomes of patients, that they assess the needs of individuals and families for services, that they use it to evaluate the performance of their providers, and one stated

that they use it to conduct research specifically to look at the cost-benefit analysis of testing.

I thought it was interesting that the top three responses here do somewhat correlate with the top three responses of the long term follow-up activities that are being performed. Next slide, please.

And then we asked how long do you conduct long term follow-up? As you can see here, there is a wide variation of length of service based on the condition, and we highlighted six different state responses just to really illustrate that point. And even though we've already heard about this is the system and it should be a system for a lifetime, only 25 percent of states are conducting long term follow-up for the lifetime of the individual. Next slide, please.

Then, in addition to assessing the current state of long term follow-up activities, we also wanted to be able to identify the challenges and barriers that exist to the implementation of the long term follow-up program.

As you can see here many different responses, and it shows that we have some work to do in this area. Standardized recommendations, definitions, and guidelines were selected in over half of the responses, and I should state here that they could pick more than one response.

And although this doesn't have a slide, we also asked the people that we surveyed what NewSTEPs could do to provide assistance in developing or helping to maintain a long term follow-up program. Next slide, please.

We allowed the individuals that we surveyed to comment and we pulled out five responses that we thought you would find interesting. Many states expressed frustration with the lack of support for implementing or expanding their long term follow-up from program leadership. They are telling us that program leadership just does not consider this a priority. However, those of us in this meeting today and those who work in newborn screening know that long term follow-up is a very critical component of the

newborn screening system. And, in fact, this committee back in 2008 stated, "All of the conditions identifiable through newborn screening are chronic and therefore require medical care and intervention throughout the affected individual's lifetime." Next slide, please.

So, what is APHL's role in long term follow-up? Next slide, please.

Again, I would draw your attention to a quote from Dr. Alex Kemper, et al, also from 2008 that basically says, "Newborn screening is intended to be comprehensive, including not only screening and diagnosis but also long term follow-up care through the medical home." So, interesting that Dr. Brosco, you're right, everything has been set for us already, right?

In addition to this, the taskforce plans to develop a manuscript on the publication of -- for publication on the status of long term follow-up currently to *The International Journal of Neonatal Screening* for their special edition for follow-up, and in addition to that, we also hope

to develop a position paper identifying a role for APHL and long term follow-up to develop a definition -- remember I told you that there still really isn't a set definition -- to develop that definition for long term follow-up and/or to identify those key components of a long term follow-up program. We're also considering developing a long term follow-up fact sheet for programs to use to demonstrate the importance of long term follow-up to their leadership and also to offer technical assistance to those programs who want to develop and implement a long term follow-up system as well as those who need and want to maintain and enhance their current long term follow-up program. Next slide, please.

Then, what is this committee's role in long term follow-up? Historically, this committee has provided insight that has really enhanced and improved state newborn screening programs, and this is an open-ended question to you. We would be happy to hear any feedback and suggestions from this committee. And then, next slide, please.

Last but not least, some acknowledgements. You can see here the various participants in our workgroup, which is continuing to work. Big thank you to Jo Ann Bolick from Arkansas and Lani Culley from the Washington State Newborn Screening Program for co-chairing this workgroup. They have done amazing work and they believe in long term follow-up and they have been inspirational to us. And thank you to the APHL newborn screening staff, to those individuals who did the data analytics and the lovely graphics for us, to Erin Darby, who is our lead, she is fantastic. She keeps us organized, she keeps us on task and makes sure that we deliver a quality product. And last but not least, Jelili Ojodu and Sikha Singh for their ongoing and continuous support of newborn screening programs. I don't know that the APHL newborn screening staff realize how much that is important to those of us out here in the state programs.

Thank you for your time, and I appreciate the chance to be able to present this information

to you today.

CYNTHIA POWELL: Thank you, Ms. Johnson, for presenting this information. It's really helpful, and thanks to the APHL for all the work they're doing in this area.

Next, we will hear from Dr. Mary Schroth.

MARY SCHROTH: Thank you. Can you hear me okay?

CYNTHIA POWELL: Yes.

MARY SCHROTH: Perfect, thank you. Thank you for this opportunity to present to the group our work at Cure SMA. Next slide.

Just to give you a little bit of information about our organizations, Cure SMA is a nonprofit patient advocacy organization and we fund and direct comprehensive research that drives breakthroughs in treatment and care. Our focus, though, is supporting families -- patients and families living with SMA throughout the US. The organization began in 1984 as Families of SMA and then changed our name to Cure SMA, and we have many, many people on the ground. We have 36

chapters across the country that are volunteer led and that is our website. Next slide, please.

So, I wanted to begin by just providing where we are currently with SMA newborn screening across the US, and I apologize if you have gone through this previously, but I just want to set the stage for what I'm going to talk about.

So, as you probably all know, we're at 33 states that are screening for SMA, and that includes those that are permanently implemented and those that are conducting pilots. And based on some of the modeling that we've done at Cure SMA, that represents a little over 68 percent of all infants in the US currently being screened. And as you all know, SMA was added to the RUSP in 2018. Next slide.

As part of our work at Cure SMA, we advocate for implementation. We also support state labs -- we reach out to the state labs to say hey, we're here, we've got materials to share with you. Please use us. Please tell us how we can help. Please tell us how we can work

together.

One of the things that we do is we also ask states to share with us the number of patients that they screen and the number of positive tests performed or potentially the screening tests that they do. And what we've learned so far, we've had 25 states respond to us, and we recognize that 17 states were added in 2020, so many of them are just beginning to collect that data. Approximately 2.5 million infants were screened since January of 2018. Among those screened, 173 infants were identified through newborn screening, and of those, just a side note, 180 families contacted Cure SMA after diagnosis, and this represents an estimated instance of 1 in 14,000. While we know that the current literature and standard that we all accept is 1 in 11,000, but what we're seeing with this early information with about half of the states reporting is 1 in 14,000, and we could go into reasons for that.

And just so people know, we do not reach out to families. Families contact us. We ask our

providers, we ask state labs to share information and then families reach out to us as they are ready to do that. Next slide.

SMA, as you all know, has changed dramatically over the last 10 years with clinical trials, of the new treatments, and in particular, trials that involved presymptomatic infants. Newborn screening for SMA is essential to achieving best outcomes for this truly devastating disorder.

In this slide with you, outcomes from the Nusinersen presymptomatic clinical trial that demonstrate that children with two copies of SMN2 can achieve motor milestones, not previously possible without treatment, and children with three copies are able to achieve all motor milestones.

In comparison, when we're treating infants who have already developed symptoms, we see increases, we see stabilization, we see slowing of disease progression, but they may never achieve the sort of milestones that we see when

we're treating presymptomatic infants. Next slide.

This slide shares with you the presymptomatic clinical trial outcomes using Zolgensma, the gene replacement therapy, and in looking at this group, when we look at the two-copy babies who received Zolgensma pre symptomatically, half achieved age-appropriate gross motor milestones and all achieved age-appropriate fine motor milestones. When we looked at the three-copy babies, all achieved age-appropriate gross motor milestones and 14 of 15 achieved age-appropriate fine motor performance.

In the clinical trials for Zolgensma, there was not -- it was an open-label trial, there was not a control group. We used natural history data that was available and also information that was based off the Nusinersen trials. Next slide.

So, this is a slide just showing you some of the characteristics of the three treatment that are approved for SMA. As a long-time clinician, I am just blown away every day when I think about

how far we have come versus where we were prior to 2016. So, we're in a phenomenal place for this disorder.

For newborns, there are two treatment options: Spinraza and Zolgensma. Evrysdi is approved for infants over 2 months of age. And I'll just let you look through this characteristics. There are a variety of reasons why an infant may go on one treatment over another, and part of our long term follow-up goals is to better understand this disease and how treatments will impact the disorder. Next slide.

So, in response to the rapid change of spinal muscular atrophy, it's so critically important to gather data about SMA populations that I know I am totally preaching to the choir here. And Cure SMA is committed to gathering real-world data, and we have three pathways right now to collect data. I'm going to talk to you more about two out of the three with subsequent slides.

The SMA Newborn Screening Registry is a

registry available to families. Families can go in to our website for the registry, provide consent, and then answer survey questions about their child including, you know, when did the child received their confirmatory diagnosis, when did they start treatment, what treatments, did they have any symptoms at the time of treatment, and this is designed as a longitudinal registry so that families will be invited back to answer additional questions every year.

The second pathway is our Cure SMA membership database, and this is information that families provide to us when they call and they talk to us. We collect some information about patients. We also send out an annual survey and make available an annual survey that's open for about six weeks where families -- patients and families and caregivers are invited to answer questions about their experience with SMA. We also use this database to recruit for clinical trials and surveys and also gather that information to better understand the experience of

SMA over time and we share that with regulatory officials. We really try to use it to advance care and opportunities for the SMA community.

The third registry is our Clinical Data Registry, and this is a registry that we started approximately three years ago. We have an SMA Care Center Network that is growing. We currently have 19 centers that are affiliated with our Care Center Network for SMA, and those centers consent patients and clinically collect information that they document within the electronic medical is sent over to our clinical data registry. I know, Dr. Brosco, you talked about the EHR and the challenges because we don't have a universal EHR or EMR, and we totally agree with you. But we're really trying to understand and maximize moving data from electronic medical records where, in my opinion as a clinician, that's where patient data belongs, and move it over to our registry in a reasonable way that we can analyze and mine that data. Next slide.

This is some information about our --

from our membership database. So, this is patient-provided information, and the first graphic is just new contacts diagnosed via newborn screening. So, this isn't all of our new contacts, but it's just specific to the newborn screening over time. So, it's divided by months and years and we've seen a gradual increase in the newborn screening, babies who have contacted us, which we expect as part of just the growth in the states that are implementing.

But one of the things I just wanted to point out to folks is that what we -- during the early months of COVID, we had fewer infants diagnosed both clinically and through newborn screening, and we saw a lull in those diagnoses and patients coming to us. So, we also saw in our data that reflection of what we interpreted as being just decreased in-person visits and evaluations of infants under the age of 2. So, our perception is that there may be a delayed diagnosis for infants with SMA who have clinical symptoms.

In the -- on the right is the breakdown of SMN2 copy number and approximately 50 percent have 2 copies with a small percent having 1 copy, 32 percent with 3 copies, and 17 percent with 4 copies, and then some -- and it's just when positive newborn screens are sent to commercial labs for confirmatory testing, typically the highest number of SMN copy number is 4 or more. Some labs may -- as a shoutout to Wisconsin who is able to do -- distinguish between 4 and 5, but most of the commercial labs are not. So, we have this grouping of greater than 4. Next slide.

So, again, we have the Cure SMA Newborn Screening Portal Survey. So, this is -- we invite families whose child was identified with SMA through newborn screening, and the parent provides consent. They can complete the survey or they can advocate the responsibility to have their health care provider complete the survey, and that is the link to that. We receive support through our Cure SMA Newborn Screening Coalition, which is Cure SMA, Novartis, and Genentech. Next slide.

Some of the data that we've collected thus far with 25 infants, what we have are 10 percent have 1 copy of these 29 infants, and we appreciate that this is a very small number of infants. Two copies, we have 42 percent of the infants have 2 copies, 31 percent have 3 copies, and 17 percent have 4 or more.

And then, we also provided you with information about treatment status. So, the majority of the infants receive treatment. Now, there is a caveat that some infants were -- some families completed the survey prior to being able to receive treatment, but I would say that 90 percent were past that window. So, there are some families who declined treatment for their infant. Next slide.

This slide shows you information about age at diagnosis divided by copy number and also age at treatment, not timed treatment, but age -- how old was the child at the time they received the first treatment, regardless of what the treatment was. And the range for age of diagnosis

was 0-22 days with a mean of 6 and a median of -- I'm sorry -- it was a median of 6, and you can, again, these are small numbers. And then for age of treatment, the greatest of spread was at 4 more copies where we had a child who was a year and a half before they received treatment.

So, we're continuing to collect this data. We really -- we want to understand better the processes that go on. Just know that in comparison, symptomatic infants typically, from the time of symptom onset until they were diagnosed, for two-copy babies was months, typically three months. So, newborn screening is just so dramatically changing this experience as well as this disease. Next slide.

So, our future plans are to evaluate the SMA newborn screening outcomes across the real world evidence data searches -- all of our data searches that we're collecting. Things that we're very interested in time to diagnosis and how can we improve that, and I think that goes back to looking at the clinical care delivery and what

happens when the referral happens to a referral center, time to treatment, symptom spectrum, which we know is changing, and then also understanding SMA phenotype.

We historically have talked about SMA by types, and that is transitioning to talking about infants regarding them SMN2 copy number and maximum motor function achieved because many of these children being treated pre-symptomatically cannot be defined as a type in any sort of fair way. So, we've actually added a category called unspecified when we're talking to our clinicians because our older -- our teens and adolescents pre-treatment group identify -- have an identity as an SMA type, but our new infants who are getting treated pre-symptomatically are being thought of in a different way. And our community is in a transition in how we think about SMA as a disease. Next slide.

Thank you so much for allowing me to share with you our experience and our hopes and in some sense our dreams and thank you all for the

work that you're doing. And I greatly appreciate the presentations that I've heard today. Thank you.

CYNTHIA POWELL: Thank you very much for sharing this information and to Cure SMA for collecting all of this data.

Next, we're going to hear from Dr. Amy Brower.

AMY BROWER: Mia, are you -- gotcha. Hi, everybody. Thank you for the opportunity to contribute to this important panel and present an overview of NBSTRN efforts to facilitate the collection, analysis, and sharing of longitudinal data. I'll begin today with a brief overview of the NBSTRN followed by a description of our experiences supporting long term follow-up efforts and highlight new tools and resources. Next slide.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development, Hunter Kelly Newborn Screening Research Program was created to support investigations and

innovations in newborn screening. Recent efforts have explored the use of genomics in the neonatal period, conducted prospective pilots of conditions that are candidates for nationwide screening to evaluate clinical benefit, and the development of novel screening technologies for candidate conditions. Next slide.

The American College of Medical Genetics and Genomics plays a key role in these groundbreaking efforts by leading the NICHD's funded NBSTRN or Newborn Screening Translational Research Network, which is a key component of the Hunter Kelly Newborn Screening Research Program. We began our efforts in 2008 as an effort to engage a variety of stakeholders across the newborn screening system. NBSTRN has now matured into a dynamic and committed network comprised of researchers, health care professionals, state newborn screening programs, families, and advocacy groups. The NBSTRN team at ACMG is beginning it's thirteenth year with a renewed mission to facilitate the discovery and validation of novel

technologies to screen and diagnose disease, pilot new technologies and treatments, describe the ethical, legal, and social implications of newborn screening research, and collect longitudinal health and genomic data. Next slide.

Newborn screening in the United States is a multicomponent, multi-stakeholder system of prenatal education, hospital and state-based public health laboratory screening, clinician, and state-based laboratory confirmation and diagnosis, clinical treatment and management, and health outcome analysis. The NBSTRN data tools, resources, and expertise are designed to facilitate the efforts of all stakeholders and leverages each component of the newborn screening system to advance research. A steering committee and six expert workers guide our efforts and we welcome your involvement. Next slide.

The neonatal screening of 4 million newborns each year in the United States leads to the diagnosis of over 20,000 infants with a genetic condition that requires referral to

clinical care and in most cases, lifelong management. This unselected cohort of newborns reflects the racial, geographic, economic, and education diversity of our nation. This may, in fact, be the perfect cohort to help advance disease understanding because although every newborn receives essentially the same screen, other factors vary including treatment choice and the course of disease. In addition, many of the screening conditions have comorbidities including intellectual disability, and these children could receive a variety of interventions that could be tracked and analyzed to identify critical periods of development and intervention.

Because the newborn screening system in the United States so successfully and effectively screens over 99 percent of the newborns, it has the potential to provide a unique platform for understanding rare disease and lifelong outcomes. In fact, the process of neonatal screening followed by a coordinated transition to clinical care facilitates the collection of health

information beginning just hours after birth. And because the majority of newborn screening conditions require lifelong care and management, we have the opportunity to conduct prospective, longitudinal, natural history studies on a population basis with unbiased assessment

Over the last decade, NBSTRN has been involved in developing a data tool to support several landmark natural history studies and pilots that have contributed to a better understanding of the etiology, pathophysiology, and phenotypic heterogeneity of newborn screening conditions and began to provide an assessment of health outcomes for these conditions. Next slide.

We developed the Longitudinal Pediatric Data Resource to establish a common data model and provide a secure environment for researchers to collect, aggregate, analyze, and share phenotypic and genomic data in question and answer sets or commonly called common data elements, that were developed by subject matter experts. The committee's publications and Follow-up and

Treatment Subcommittee have guided these efforts including a focus on the key component of long term follow-up and the Hinton Framework. The collection and analysis of long term follow-up data from newborns diagnosed with the condition through newborn screening is important to ensure that we achieve the best possible health outcomes for these infants and the LPDR enables parents, health professional, researchers, public health teams, and advocacy groups to advance knowledge and contribute to this important goal. Since its launch in 2013, the LPDR has been utilized by several research teams and state newborn screening programs conducting longitudinal data collection of both RUSP and candidate condition, efforts that explore the use of genomic sequencing in the newborn period, and groups that were conducting pilots of candidate conditions. Next slide.

The LPDR is housed within a FISMA Moderate cloud environment and is available for use by all NBSTRN stakeholders. Key objectives of the LPDR are the sharing of findings and secondary

use of simulated data. The LPDR facilitates this data sharing and data standardization with third-party databases including the NIH's National Center for Biotechnology Information or NCBI, Database of Genotypes and Phenotypes, known as DBGAP, and the National Library of Medicine's NIH COVID Repository.

The LPDR also provides access to data dictionaries from studies that can be used to create electronic data entry forms and also features case-level datasets that are deidentified and available for data mining.

The secondary use of the accrued LPDR data may help to establish the efficacy of new treatments and management approaches, inform the community about the value of early identification and treatment for newborn screening, and identify areas for improvement in disease management throughout the lifespan. Next slide.

From coast to coast, over 100 researchers, newborn screening state programs, and advocacy groups have used the LPDR in over 30

basic translational public health and clinical research projects. The LPDR is designed to share these teams' new findings and foster the secondary use of these original datasets. Our newly launched website enables investigators to explore unique datasets, collaborate with leading investigators, and design studies using validated common data elements.

In newborn screening, the use and development of common data elements is focused on facilitating data collecting, sharing, aggregation, analysis, and dissemination. The ability to combine datasets is especially important in newborn screening because the majority of conditions are rare and accumulating enough subjects to have statistical power is often a barrier to understanding health outcomes and the benefits of early identification and treatment.

The NBSTRN website has data displays that describe the types of data and populations that are available for secondary use and our data government and data sharing policies provide

qualified users active disease datasets. Next slide.

The LPDR has been utilized in a variety of efforts including a 10-year effort to collect, analyze, and disseminate health information on individuals with one of 42 different RUSP conditions collected in 30 clinical sites located in 22 states. It's also been used in multi-state pilots of four conditions that collectively screened over 1.2 million births. The LPDR has been used in genomic sequencing of four cohorts of newborns including infants in a neonatal intensive care unit and also was used in studies that are beginning to expand the diagnostic window of newborn screening both beyond and before the neonatal period.

The LPDR also has been used recently by patient registries, so we're helping groups and advocacy groups that have developed patient registries to consolidate them into a single data dictionary that will support future expansions of the newborn screening panels.

To develop the CDE sets, we recruit subject matter experts who care for newborn screen-identified individuals. These subject matter experts make up our clinical integration group, which includes mostly [indiscernible 2:17:42] and plays a key role in defining the type of information that would be useful to collect.

As the datasets contained in the LPDR grow, we hope that health care teams can utilize this information to inform their clinical decisions. The NBSTRN Clinical Integration Group has generated CDE sets containing over 24,000 data elements across 75 conditions. The CDEs have been used to develop electronic case review report forms and have been utilized in a variety of research projects, resulting in case-level data for over 8,000 subjects with an average of four data collection time points per subject. Next slide.

As the data accumulates, it becomes more useful. An example of this is our recent work with the Inborn Errors of Metabolism Consortia.

The initial IBEMC effort enrolled over 2,000 subjects across 42 RUSP conditions, utilized an average of 7,000 CDEs per condition, and collected longitudinal follow-up or data collections. These LPDR datasets contain a lot of questions but importantly, they contain what expert clinicians thought were disease-specific questions to ask longitudinally. So, we think it's sort of a starter set for what could be asked longitudinally. Next slide.

So, the IBEMC effort informed a related effort with the National Coordinating Center for the Regional Genetic Network, which worked with state newborn screening programs and public health departments to think about instead of asking many, many questions to really learn more about diseases and outcomes, what could we empower state programs to do?

So, we met in 2013 and brought together many clinical experts and state programs and looked through these many, many question and answer sets, and we actually came up with a

consensus set of four minimum questions that could be used by newborn screening programs to conduct long term follow-up data collections. Next slide.

The NBSTRN recently launched a new website designed to expand our tools and resources. This improved website furthers the NBSTRN's mission to foster collaboration among newborn screening stakeholders and facilitate research. In addition to the case-level datasets and expanded CDE sets in the LPDR, two new tools were developed that provide key information and specifics and foster collaboration across stakeholder groups. Next slide.

Currently, newborns in the United States are screened for 81 disorders, 61 RUSP conditions -- including 61 RUSP conditions. In addition, the screened conditions, there are thousands of rare disorders that may be candidates for newborn screening. This tool, the Newborn Screening Conditions Resource, provides a centralized resource of facts and statistics on both screened and candidate conditions. This tool is designed

to be an interactive resource for researchers, clinicians, parents, families, and advocacy groups to learn more about these disorders, and it provides links to the National Library of Medicine and NCBI resources. NCBI importantly provides access to biomedical and genomic information and maintains MedGen and CBI's portal to information about human disorders and genotypes that have a genetic component. Using a filter tool -- filter module within this tool, you can sort conditions by nomination and ACHDNC category. Next slide.

Because newborn screening programs play a critical role in expanding the number of screen conditions, by participating in research and research pilots and by providing access to residual samples and data, the NBSTRN created a new tool called the NBS Virtual Repository of States, Subjects, and Samples. This NBS-VR provides national and state-level views of policies and procedures of interest to researchers, clinicians, families, and advocacy groups. The NBS-VR gives users insight into the

number of conditions screened in each state or territory, the number of expected cases, and the incidence rate of conditions that are currently part of nationwide screening or conditions that are candidates for pilots. This tool also details the number of births per year and the distribution of race and ethnicity by state. Eight percent of newborn screening programs retain samples longer than one year and the NBS-VR helps researchers request these samples for their studies.

Twenty-three newborn screening programs screen for conditions that are not currently part of the Recommended Uniform Panel and this tool enables providers, families, and advocates with a link to additional information on these conditions. In addition, this tool provides easy to navigate visual summaries of key statistics and enables clinicians to connect with their local newborn screening program. Next slide.

The NBSTRN team has worked with the National Library of Medicine, who is creating a repository of CDEs to facilitate data sharing.

The NIH CDE Repository currently catalogs over 26,000 elements across 16 classifications with multiple NIH institutes and efforts being represented. The NBSTRN work is represented within the NICHD module. This repository is designed to allow researchers to build data collection instruments from shared CDEs and also to contribute generated data elements.

To foster the use of these standardized CDEs, NBSTRN deposited question and answer sets within the NICHD module and these are now available for use by the research community. Next slide.

The ACMG team is committed to enhancing the NBSTRN data tools and resources to support the multiple stakeholder groups and environments within newborn screening and to help accelerate discoveries. We look forward to working with the committee on future initiatives and are happy to provide any additional information that would be helpful. Next slide.

Thank you to the NICHD for funding,

supporting, and guiding the development, maintenance, and enhancement of the NBSTRN. Thank you everybody.

CYNTHIA POWELL: Thank you, Dr. Brower, and thank you to all of our panelists for your excellent presentations today.

Now, I'd like to open it up for questions or comments from our committee members followed by organizational representatives. Scott Shone.

SCOTT SHONE: Thank you, Dr. Powell. So, Jeff, I have a quick question about -- thank you everybody, let me start with that. Jeff, I have a quick question about your comment on equity. It really jumped out at me and maybe it's for Annamarie, because I want to make sure it got it -- I understand it because my comment will depend on if I followed it right. It seemed as though there was a suggestion that we can't solve all the equity issues, so we should just move ahead with whatever it is, in this case newborn screening disorder, and that equity should or does follow. Did I -- can you just clarify that for me and make

sure I got that right before I --

JEFF BROSCO: So, let me say a couple -- is it okay if I speak, Cynthia?

CYNTHIA POWELL: Yes, please. Go ahead.

JEFF BROSCO: Jeff Brosco, committee member. So, let me try to say it more clearly and then maybe Annamarie can jump in. You can imagine sort of two extremes. One is yes, we have newborn screening, but the treatment is either so expensive or so rare and so impossible to find that why bother for newborn screening because the treatment is there but nobody can get it. And at the other extreme, it might be that yes, we have a perfect system that works great and every single child who is identified immediately is available for treatment, follow-up clinical and otherwise. So, the question really is somewhere in the middle, what happens? So, if we said yeah, 80 percent of kids who get identified can get treatment, we'd probably be comfortable with that. But as it starts moving further and further away, it's harder, and I'm remember specific

conversations, less at the national level and more at the state level, where families would basically say, and advocates and clinicians, yes, I know we can't get this to everyone in the state right away, there aren't enough commissions, insurance isn't paying for it, whatever the issues may be, but we can help these children right away, so why wait. So, that's sort of one argument.

The argument from equity is well, that's simply not fair and we need to make sure that if we're going to do a public health program where we're identifying theory and every infant has a commission, we have some responsibility, either as a state or as a society, to get treatment in place. And I think Annamarie can speak for herself, but she made a really eloquent argument for that first side, which is if we can help 40 or 50 or 60 percent of kids, we should do that right away and that can spur reaching out to the kids who aren't reached right away. Maybe she should say what she's saying better than I can.

CYNTHIA POWELL: Annamarie Saarinen.

ANNAMARIE SAARINEN: Thank you. Annamarie Saarinen, committee member. I don't know that I can say it better than that, but I'll try. What I was trying to get at -- well, there's two different pieces. One is sort of how we -- how these numbers and the information we know today impacts how we're evaluating and moving things through the nomination and evidence review process. So, it's hard for me to separate the two because for that one, I think all of these considerations come up, you know. For me, as someone who is trying to look at all the evidence and the data because, I think I've mentioned before, I'm sort of an advocate for thinking about how provisional acceptance of conditions on the front end, right, just even at the early -- from moving from nomination eval into evidence review, that that is a pathway we can and should be considering because sometimes that is the only way to get us from point a to point b. So, without provisional acceptance or provisional addition, that patient population will struggle to meet all

the criteria or to come up with the evidence required to checkmark that box. So, I'm just going to say that on the front end of things.

But what I was trying to get at on the other side was that the suggestion that we should wait to add something that has -- ticks off all of the baseline evidentiary requirements because we know we might have an access to treatment issue or what we would call a gold start equity mark, to me feels substantively wrong because then, if you just from an ethics standpoint, you would be talking about denying access to those who can, in the present paradigm, get access, right?

So, we're saying -- so, if there's 50 percent of kids, we'll say like yeah, but you shouldn't be able to get an early diagnosis and access to care because we have 50 percent that are going to be challenged to get that now. And so, where, you know, how does that play out from a -- just from an ethics standpoint, right?

So, my experience in newborn screening for congenital heart disease, particularly in

resource-poor settings now -- and I hope I can just bring that in as an example -- is that the data is the evidence that's often required, and it can drive the advocates and the policy-makers to make the improvements that are required. But if we don't sort of move forward based on what we have -- again, like letting the perfect be the enemy of good -- that's -- I think that's a real challenge that we have. We're basically denying -- denying the opportunity for a better outcome of survival for a subset because we haven't reached that perfection on the equity side yet. And I really have seen this happen in practice in, you know, very resource-challenged settings where once you provide public health the information on startup programs, that they start getting the data, that they actually will make investments in treatment infrastructure. And, I mean, the optimist in me says that that actually works and that can continue to happen even in someplace like the United States that has more.

While I have the mic, I'll just be really

quick to thank Amy Brower. That was an excellent presentation, and it really like reminded me how important the NBSTRN is to the work of this committee, and I almost feel like we should have -- - again, this is a suggestion, take it for what it's worth -- I almost feel like we should have a placeholder in every meeting to do a like micro report from NBSTRN because this data you provide is so useful and it can trigger so many actionable things, not just for the primary committee, but for the workgroups. So, I want to thank you for that, Amy, and thanks for all the good work.

AMY BROWER: Yeah, thank you. We'd be happy to do that.

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Hi. My question is for Dr. Schroth. So, you mentioned that you have three pathways to collect the data for the registration. I'm just wondering, did you think sometimes that could be overlap? I mean, do you have a structure in place to be sure the children were not coming twice?

MARY SCHROTH: Yes. So, the Newborn Screening Registry overlaps with the Clinical Data Registry. So, the Newborn Screening Registry is patient-reported outcomes, but it does overlap with the clinician-entered data. Separately, we have our membership database. We are able to cross-match all of our databases together because they're all owned by Cure SMA. So, yes, when we do reporting, and we're starting those analyses now looking at what data we have across our registries, but our intent with our registries is to not double count patients. So, within our registry, we have -- well, within the Clinical Data Registry, we have PHI, and then we have PII in our membership database as well as in the registry. So, we have that ability. But our plan --

MEI BAKER: Thank you.

MARY SCHROTH: -- is to not share that personal identifying information externally.

MEI BAKER: Yeah. Thank you. I thought you would. I just wanted to confirm.

MARY SCHROTH: Thank you, Mei.

CYNTHIA POWELL: Scott Shone, did you have another question?

SCOTT SHONE: Thank you, Dr. Powell. Yeah, I didn't -- thanks to Jeff and Annamarie for clarifying. My -- my -- so, I guess my comment -- I have more of a comment than a question, which is that I think that the comment of letting the perfect be the enemy of the good, it seems like we have good. I think we still have, you know, reflecting on the disorders that we have in our -- I just feel that in our health care public health system, we -- we achieve something and we move on, like we're already looking to the next disorders and the next disorders. So, I think it requires -- it is more -- more important that we have to look back at what we've done and add the equity piece to that assessment, right? And we talked about it, but I think Jeff's comment in the preamble to here requires that because the same groups continually get left behind, whether it's newborn screening or any other public health

problem that we are seeing, and it's so exacerbated by this pandemic.

So, again, not that newborn screening saves all, but we have an obligation to look at this in what we've already done that we still have immunology deserts dealing with SCID ten to fifteen years out. We have treatments that are more costly and more costly. We're only -- we're creating the gap between equity and fairness and good and perfect even broader. So, we absolutely have to bear this in mind. That's -- that's my comment is that we -- and I'm not suggesting we're not -- but I do -- I don't necessarily agree with the if we build it, equity will come.

ANNAMARIE SAARINEN: I know there's an order here, so I'll just reply to that since I wanted to ask Scott, but I couldn't find the chat place to say did I send my answer to the question. So, I 100 percent agree with you on the evaluative piece, 100 percent. And this is where, I mean, not to sort of connect or weave a thread that might sew everything together, but this is where

like the stuff that NBSTRN is doing, I do think provides such a valuable platform to do that sort of analysis and I don't know that we have as much -- well, or all of us anyone -- have as much visibility into that that we maybe should or might like to. But that's exactly what I was saying. I think my fear is that we -- and I do -- I do believe in my Pollyannish way that if you build it, they will come to a degree, but you can't just build it, have them come, and then not ask them how their experience was when they leave the ballpark.

So, it truly -- you have to go back and look, and you have to use that data to either improve the program to make those necessary adjustments or say like holy crap, this didn't work like we thought it was going to, and I think that's very fair. So, I want to agree with you on at least 75 percent of what you're saying.

CYNTHIA POWELL: Thank you. Robert Ostrander, I've seen your hand raised earlier, but I don't see it now. Did you have a comment?

ROBERT OSTRANDER: I really did not. I mean, I had a little minor one, but I think I just bumped my hand up anyway. So, I appreciate you recognizing me, but for once, I'll keep my mouth shut.

CYNTHIA POWELL: We appreciate your comments. Natasha Bonhomme.

NATASHA BONHOMME: Great, thank you. I have a couple comments and I think a couple questions. But, you know, Scott really covered a lot of what I was really itching to say. You know, it really -- we can't start to have a conversation -- a true conversation around health equity until we really acknowledge that when we say, oh, there's the 20 percent or the 50 percent. It's always the exact same kids and it's the exact same families. And if we can't acknowledge that, to me, it feels like a very thought experiment as opposed to what is happening with real families. So, I appreciate Scott for saying that.

I also really wanted to acknowledge the data that was presented from SMA. It was -- I was

really excited to see that data because I feel like, phew, we really are seeing data from the full system, especially the part of the system that often times is left to support the families and to be able to have that data was really refreshing, and I really applaud -- applaud you to have that infrastructure to capture that data, because it is a lot, and a lot especially to put on the patient advocacy organizations. So, really great work happening there, so thank you for sharing that, and I hope that we can see something similar for many of the other conditions that we tend to talk about.

And now to my questions. It was great to get this update from LPDR and the visuals are beautiful and it's really great to see how these different pieces are being connected. I guess one question I have in the realm of this conversation about health disparities and what we're learning, do we feel like now with these amazing tools, both through NBSTRN and other places, that we are closer to being able to answer some of the

questions that we've been asking for quite some time around are our outcomes better, you know, are there disparities, where are the disparities, how are we addressing them? You know, I think because the exciting part about building tools is being able to implement them and to be able to say, gosh, ten years ago, we couldn't answer this and now we can. So, just wanting a bit on that.

And then lastly, my last question, I guess it's directed to Carol around the great work around long term follow-up and really thinking about that. Could you speak a bit more to kind of -- I apologize that when the slides were going through, I was not able to look at them -- kind of like that connection around the work that has been happening and will be happening through this workgroup around long term follow-up and is that like really focused from the lens of the public health programs, is it from a lens of, you know, long term follow-up, you know, from a systems perspective? If you could just highlight that, that would be great. And I think that's

everything for now. Thank you.

CYNTHIA POWELL: Thanks. Amy Brower, do you want to respond to Natasha's first question?

AMY BROWER: Sure, sorry about that. Yeah. So, I think, Natasha, what you point out is that the more data we have, the more useful it is, and that's what we've seen over the years. But as we presented, you know, this is such a unique opportunity in newborn screening. Every newborn gets screened, but we can't follow every newborn. What we've learned over the last several years is, you know, we are project-by-project, disease-by-disease. We've got such an amazing range of, you know, ages. So, we have from newborns all the way up to 80-year-olds. So, as the data accumulates, it's really becoming useful. But are we getting everybody? No, we're not. And can we start to answer some questions? Sure, we can, but you know, again, it's disease-by-disease. I would love to be able to follow, you know, very condition in the way that we follow now Sickle Cell, you know, SMA, you know. We've got projects

where we're helping states conduct annual check-ins, and I think that's a good step. So, I think we're getting there and we're making steps, but I don't think we're anywhere near addressing some of the issues that the committee has brought up.

NATASHA BONHOMME: I guess just to add to that, I can definitely appreciate that, and I do think more data is helpful. But I think what's also really helpful is really understanding how we're asking certain questions, and I think that's something we're all learning, especially from the lens of health equity is, you know, it's having the data but also asking the question and then being like, oh, I guess I asked this question, but I actually meant this question, and really building upon it that way. So, I think really having a focus on both would be great. Thank you for your response.

CYNTHIA POWELL: Carol Johnson, do you want to respond?

CAROL JOHNSON: Yes, thank you, Dr. Powell. So, Natasha, early in the presentation, I

talked about how there was a lot of discussion and we ended up having to focus on two separate projects. I think our list was extremely long and encompassed both what's kind of that -- what's in front of us, what do we need to work on today, as well as the system, as you mentioned. That said, we would love to hear from you any ideas or recommendations that you would have would be very much helpful. I do think, you know, we have some ideas for what we need to work on in the future, but maybe those aren't what we should focus on right now. Maybe there are some other ideas that you might have, and again members of this committee might have for us as to what -- what to do next. Did that answer your question, Natasha?

NATASHA BONHOMME: Yeah, and I think that it's important to kind of think about, you know, these questions from all the different viewpoints, I think, as has been said.

CAROL JOHNSON: Absolutely.

NATASHA BONHOMME: I think it's been said about 50 times today, newborn screening is a

system with lots of different parts. I think that's great and so exciting to see that.

CAROL JOHNSON: Right. And that's why it was so overwhelming in the beginning to try to decide what to focus on, right? So, yes. Thank you.

CYNTHIA POWELL: Jed Miller.

JED MILLER: Yes, hi. Jed Miller, Association of Maternal and Child Health Programs. I have a question for Carol Johnson regarding the Landscape Survey. One of your slides presented about eight respondents who track the number of individuals lost to follow-up, and I'm just curious, were any comments -- and this is, I guess, a question for you or anybody else here, you know, on, you know, on the panel -- is -- did anybody volunteer any information about dedicated programs or efforts to try to find those lost to follow-up to, number one, discern if they are truly lost or just administratively lost? For instance, you know, if somebody moves out of state or out of the country, changes providers, or just

something in that there's a disconnect, but they don't actually -- they actually aren't lost versus others who truly are lost and who really need help, and there's a lot of factors that go into that. I'm just kind of curious if any knowledge was shared with you or if anybody else knows, thanks.

CAROL JOHNSON: Is it okay to go ahead and comment, Dr. Powell?

CYNTHIA POWELL: Oh, yes.

CAROL JOHNSON: Okay, I just wanted to make sure. So, I don't know that we have that level of granularity in this survey. Different programs do different things to track their lost-to-follow-up. Some programs have a very active and robust way that they track those. I can speak only for my program right now, but we do a weekly review of birth certificates versus newborn screens, and we absolutely do act to follow up to try to get those babies in to be screened, and we believe we're at about a 99.6 percent rate of at least being able to determine what happened with

that baby, and that includes, you know, the refusals that we receive as well.

It is -- it does vary program-by-program, and this is my shameless plug for the new CLSA Follow-up Guidelines that are going to be adopted in the near future and working toward some minimal standards in follow-up, and that is one of them, and it's important, and that is why it's one of our quality indicators.

JED MILLER: Thank you very much.

CAROL JOHNSON: You're welcome. Thank you.

CYNTHIA POWELL: Chris Kus.

CHRIS KUS: Yes. A general question and it's at the end, and I know, but I'd be interested in the panelists' comments about a general question about have we made progress regarding newborn screening long term follow-up over the past five to ten years and what do we need to do to make progress?

CYNTHIA POWELL: Anyone want to take that on? Dr. Brosco, I'll pick on you.

JEFF BROSCO: That's totally not fair because Chris and I were talking about this was a great question, so I said you should go ahead and ask it. I'd like to hear actually from Carol Johnson and maybe in particular a little bit about what you've already reported on, but also how NewSTEPs might fit into this. You know, is there a way to extend or what kinds of things APHL could do. One of the things that really impressed me was a number of states seemed to say we need -- we need standards, we need a mandate, we need -- you need to tell us what we need to do.

CAROL JOHNSON: Correct. I absolutely believe that to be true, and I speak on my own behalf that people are looking for guidance, they're looking for help, they want to know -- newborn screening programs really want to do the right thing, but sometimes they have so many barriers, as you saw in those slides, that they can become insurmountable, right? So, I think, yes, minimum standards, guidelines, what are the elements of the long term follow-up program, and

you could ask, you know, the 54 states and territories and perhaps get 35 different answers, right? So, again, that comes back to we do need to set some -- some standards and then from there, we have to be able to convince the powers that be that long term follow-up is actually not an add-on component of newborn screening but an essential component of newborn screening.

AMY BROWER: And I guess -- and I'll jump and say, you know, I think some of the things are true, if you build it, they will come. So, you know, luckily we've been funded to build some tools and infrastructure, and we've seen state programs come to us. We're working with several right now, you know, who are particularly interested in subsets of the RUSP or, you know, and that's the great thing about newborn screening as a geneticist is there are so many diseases. Without the tough part, there are so many diseases, and so, trying to build a system where you can really understand more about the diseases. You know, we're learning so much about SCID, about

Sickle Cell, about every single condition on the RUSP as we collect this data, and it's such a missed opportunity that we don't have a national system to follow these children, whether it's letting parents, you know, enroll, letting states follow them, encouraging clinicians to follow them. You know, there's just so many ways that we could do this, I think.

CAROL JOHNSON: Right. And I'll make another comment and that is that we have some programs that are really struggling just to call out abnormal results, right? And so, I don't know what comes first, and this goes back to this overarching theme for today's talks is that if you build it, will them come, and we also have to fix some things that we're already doing, right? And that is to appropriately staff and fund follow-up activities, whether that's in the short term follow-up or long term follow-up.

CYNTHIA POWELL: Debra Freedenberg.

DEBRA FREEDENBERG: Hi. I was just going to add a little bit more to Jed's question to

Carol as one of those participating programs. And Carol is quite right. Each program does choose what they want to do, but I know that like, for instance, before a child is placed in the long term follow-up category -- lost to follow-up, excuse me -- lost to follow-up category, there is a great deal of effort that is expanded into finding that child, finding out what happened to them, did they switch states, did they go to another provider, was there a loss of just contact, and there is a great deal.

Now, I can't say that happens for every program, and then there is a review of those children that are going to be put in that category before they're actually put into that category. So, there really is, you know, from the state that I'm involved with, a great deal of effort that's expanded -- expended, excuse me, before a child would be put into that category, and they're only put into that category very reluctantly. It's not viewed as a positive to have to put a child into that category.

CYNTHIA POWELL: Melissa Parisi.

MELISSA PARISI: Can you hear me?

CYNTHIA POWELL: Yes.

MELISSA PARISI: Okay, thanks. I just wanted to make a quick follow up comment to this recent discussion and, in particular, Amy Brower's comment. I mean, you know, from a research perspective, I think we all would agree that every child identified with a newborn screening condition, in the best of all possible worlds, would be automatically enrolled in a long term follow-up research program where we would track and acquire the information that we need to really understand the natural history of these conditions. I mean, given that they are rare disorders, you know, we're just scratching the surface when we nominate and vote to add a condition to the RUSP.

So, you know, to the extent that some of these systems can be put into place such as through the, you know, APHL NewSTEPs or the NBSTRN to allow for the accumulation of data in a

deidentified manner, even, in a way that can help inform our understanding of these disorders, that, in my mind, would be win-win and help us get towards this path of creating true equity for these conditions and these kids who are affected.

CYNTHIA POWELL: Thank you. Robert Ostrander.

ROBERT OSTRANDER: So, now I do have a quick comment, and this came from our discussions in our workgroup a couple of years ago when Joe and I had talked about again this federated system, and I think one of the potential resources that we're overlooking is the specialty centers for a number of these conditions. I mean, that is a nationwide network, to some extent, because I think these specialty centers communicate with each other pretty regular, if nothing else, at national meetings and reading each other's papers and literature.

And it seems to me that that -- we should tap into that as the basis of federated system and, you know, to the comment that, you know, Jeff

carried forward from our group, whose responsibility is this? I think we should think about ways to make that part of the responsibility of specialty centers is collecting a, you know, dataset on these various conditions that, you know, are under their various purviews, thinking about that diagram. You know, there are probably some universal questions that apply to every kid. There are some questions that apply to kids with special health care needs. There are questions that apply to all kids diagnosed through newborn screening, and there will be disease-specific questions. And again, if we could somehow suggest that this is the responsibility, especially centers that have some sort of national clearing house that would collect that data, and maybe even design the, you know, what are we looking for questions. I really think we should strongly think about that.

Again, I don't know what purview of this advisory committee is in terms of advising the Secretary to perhaps set up a clearinghouse, but,

you know, I didn't -- we've heard of a lot of people that are potential -- potentially providing data. But I think that specialty centers is just the right size and shape as a potential data source for a lot of these things.

CYNTHIA POWELL: Well, if I can comment as someone from one of those specialty centers, while I think that's a great idea and a great way to do it, similar to the public health labs, we're stretched so thin, you know, we can't, you know, hire new people to enter that data. We just don't have the funding. So, it's all coming down to how do we fund this both with the laboratory as well as the clinic levels.

ROBERT OSTRANDER: No, no. And I certainly agree, and that's where I wonder where you're, you know, how far the advisory committee can go in terms of suggesting that. I mean, suggesting that it be done is one thing, but when you suggest something be done, it's best to suggest a how, and obviously money -- money is an issue. But, you know, the specialty centers

around here and the pediatric departments for the NICU graduates do a wonderful job of gathering data and all their NICU graduates longitudinally through their lifetime up until 18 and, you know, that's the kind of model that made -- made me think about this is what the NICUs do.

CYNTHIA POWELL: I know, and I think, you know, there's similar things that they do for pediatric cancer and follow-up of those cases, and that's one reason, you know, they've made such great advances in treatment. So, I think we really need to start looking outside the box, so to speak, you know, to figure out ways how others have funded this and how we might go about suggesting how this be funded.

I know we're running short of time. Let's see, Jennifer Kwon, you haven't had a chance to speak. Go ahead.

JENNIFER KWON: Thanks. I actually just lowered my hand because a lot of what I wanted to say -- but I will respond to Chris' provocative question with a provocative answer. I -- I don't

know that we've made great progress in long term follow-up for all of the reasons that we've heard. I think we've made incredible progress in making treatment advances available to children with rare disorders. I think that that's been sort of the core job of this committee, and you've done a great job. I just -- I think that the long term follow-up is such a key piece, as we all know, and I think that people are just scrambling about how to address that need. So, I recognize that. I wish I had some ideas, but just that comment.

CYNTHIA POWELL: Thank you. Annamarie.

ANNAMARIE SAARINEN: Hi, thank you. Annamarie Saarinen again. I was -- I've been really listening to everyone's comments, and they're all just very valuable and spot on. But I was trying to think of it as like we're asking a question and is there a model and sort of like the way recovering lobbyists sort of think about things. And I did pull up -- and I'm sure it's on the website -- the letter both from Chairman Powell to Secretary Sebelius back in 2010 and then

the reply letter back from Secretary Sebelius. There was more than one, as you might recall, for CCHD screening. But what I loved about that letter from the Secretary back to this committee was that it came with an action plan. It didn't come with necessarily dollars connected to the action plan, and I think that may be the missing link here, but it basically said like the following things need to happen as we implement a new condition onto the panel here, and they fell into the buckets of research, surveillance, screening standards and infrastructure, and education and training, and under each, it basically said HRSA shall do this, CMS shall do this, FDA shall do this, NIH shall do this and some of them were kind of time-bound, but as I look at them, I can see which ones -- we could say like yep, that actually happened, but I see ones that I can, I don't know, I feel like I can say like that didn't happen or that hasn't happened in a way that was useful in coming back to this committee to say upon implementation of this

screening as it rolled out, what pieces are still missing that may impact access, equity, and outcomes for children affected by that disease?

But I do think there are some models out there. I would even consider looking at this, you know, Reauthorization of the Newborn Screening Saves Lives Act. What can be embedded at the policy level to ensure that the fiscal and human burden of doing the things that need to be done when these conditions get out, it doesn't fall on programs that are currently underfunded and understaffed to be able to do it? And I think, at the end of the day, it all comes -- it all comes down to money, and if you don't fund -- and that's why I use the word infrastructure -- that's what it is. It's about money and funding.

So, I guess I would encourage us to look at some of these things that are already embedded in the way HHS has thought about newborn screening and how, at least for CCHD, that came back with like a set of deliverables that were supposed to address some of these issues.

CYNTHIA POWELL: Thank you. So, we're running out of time. Mei Baker, Melissa Parisi, and Jed Miller, and then we'll need to stop.

MEI BAKER: I just wanted to make a very quick comment for the long term follow-up. I heard so many good ideas in listening, and I think I want to echo what Melissa was saying. Like, ideally, actually I think we should make it a goal, not just -- like ideally, we will start with newborn screening. I think we need to set the kind of goal to do that. Otherwise, we will never get to the point where we need to be. And the one thing I just want to emphasize when I heard this is the connections because I think that, you know, we heard Amy have the wonderful presentations. I think she did an amazing job to reach out all this, you know, specialties and conditions. And coming back to the newborn screening program, and I can tell my personal experience, after short term follow-up, continuing to have the connection with the clinical can somewhat a little bit -- I just -- I don't know what words to put it in

because the incentive is not there and also I think the newborn screening alone is just -- to me, it's very, very hard to achieve the minimal longitudinal study.

And another thing I want to make comment is because NBSTRN comes across like research. This is a kind of -- sometimes kind of becomes a little bit difficult for the program to get the connection. So, I was hoping [indiscernible 3:02:24]. I was thinking like a newborn screening because CDC pretty much is doing like the testing part, follow-up, and most of the NewSTEPs part. So, it's kind of a little bit of a consortia in a way and really emphasizes [indiscernible] and also, I think, we talked about the policy importance. It really comes across, I mean, program evaluation. So, I think then, of course, during the process, we will address a lot of research questions. I think maybe we can think about this around program evaluation to become an obligation, become as a part of what we need to do. Thank you.

CYNTHIA POWELL: Thank you. Melissa Parisi, did you want to say anything? Maybe not. Jed Miller.

JED MILLER: I apologize. That was inadvertently still up from before. Thank you.

CYNTHIA POWELL: Oh, okay. Thank you. Maybe Melissa's was also.

MELISSA PARISI: Yeah, same for me. I'm sorry about that.

CYNTHIA POWELL: Oh, no problem. Thank you. All right.

Thanks again to everyone and this was, you know, a really great session. I appreciate all your input and we'll, you know, take all the comments under consideration as we think about, you know, how we move this forward and what steps we can take to make it happen.

NEW BUSINESS

Is there any new business? Do committee members have any announcements or new business at this time?

All right, not hearing any or seeing any

hands raised, then I want to remind everyone that our next meeting will take place May 13th and 14th, 2021, and the February meeting of the Advisory Committee on Heritable Disorders in Newborns and Children is now adjourned.