Health Resources and Services Administration

Advisory Committee on Heritable Disorders in Newborns and Children

Meeting

9:30 a.m. to 2:00 p.m.

Wednesday, April 24, 2019

Reported by:

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C O N T E N T S

P R O C E D I N G S

CHAIRMAN BOCCHINI: We are ready to begin today's meeting. All right. Welcome to day two of the Advisory Committee meeting. I want to thank you all for your support yesterday and hope everybody had a good evening, and we're ready to start today's agenda.

So, first we'll being with the roll call. Today, for committee members, Kamila Mistry is by webcast. Kamila, are you on? Okay, we'll come back. Mei Baker.

DR. MEI BAKER: Here.

DR. JOSEPH BOCCHINI: Susan Berry.

DR. SUSAN BERRY: Here.

DR. JOSEPH BOCCHINI: I'm here. Jeff Brosco is unable to attend today. Kyle Brothers.

Dr. KYLE BROTHERS: Here.

DR. JOSEPH BOCCHINI: Jane DeLuca.

DR. JANE DELUCA: Here.

DR. JOSEPH BOCCHINI: Carla Cuthbert.

DR. CARLA CUTHBERT: I'm here.

DR. JOSEPH BOCCHINI: Kellie Kelm.

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: Joan Scott.

MS. JOAN SCOTT: Here.

DR. JOSEPH BOCCHINI: Cindy Powell.

DR. CYNTHIA POWELL: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi.

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen.

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH BOCCHINI: Scott Shone.

DR. SCOTT SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini.

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: And our DFO, Catharine Riley.

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: For our organizational representatives, Robert Ostrander.

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: Debra Freedenberg.

DR. DEBRA FREEDENBERG: Here.

DR. JOSEPH BOCCHINI: Michael Watson.

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: Britton -- Britton Rink -- Rink by webcast.

DR. BRITTON RINK: Here.

DR. JOSEPH BOCCHINI: Jed Miller.

DR. JED MILLER: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley.

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus by webcast.

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Natasha Bonhomme.

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: Siobhan Dolan.

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: Cate Walsh Vockley.

MS. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: And Shawn

McCandless. And, go back to Kamila Mistry. All right. Thank you.

So, first on the agenda is a presentation on Newborn Screening Pilot Studies. Dr. Michael Watson will make this presentation. He is Executive Director of the American College of Medical Genetics and Genomics and Organizational Representative to the committee. Pilot studies are a critical component of the evidence review for conditions nominated for the RUSP. In 2016, the Newborn Screening Pilot Study Workgroup of the Advisory Committee presented a report to the committee, and the committee adopted those recommendations for the minimum pilot study data required to move a nominated condition into Evidence Review Process and has used those criteria ever since.

Dr. Watson and a team of experts have now been working on a comprehensive review of the necessary components of pilot studies for newborn screening, and he will share this work with the committee today. So, Michael, thank you.

NEWBORN SCREENING PILOT STUDIES

DR. MICHAEL WATSON: All right. Well, thank you. This is almost an anti-climatic day for you, isn't it? Had the party yesterday, and now Cindy better watch out for what's coming. I'm appreciative of all the regrouping that the committee is doing. I think it's a -- it is a good time given all the changes that are going on, and we'll talk a little bit about some of those changes that are happening.

So, even though I am the Executive Director of ACMG, this is largely an NBSTRN perspective. We've been working on these pilot studies -- a number of pilot studies for quite a while now and have learned a fair bit from our experiences with these. It fits into the NBSTRN mission and, in fact, we work a lot on conditions that are -- we've had issues with the common rule about what their status is when we talk on the pilots, whether it's an implementation pilot or a pilot to really understand and develop the kind of data this committee needs to make its decisions.

But it does fit. We deal with new technologies, new conditions, new treatments and management approaches. In this area of pilot studies, we do obtain un-biased -- I think the important thing is to obtain un-biased information, and newborn screening really is the first place where we get a real taste of what something looks like in a general population setting instead of the biased perspective that we bring into these pilot studies that are based on the people that present for health care typically more severe than what the condition really is.

So, this pilot piece that gets you at the un-biased population is really critical, and we're in the business of validating new tests and treatments in asymptomatic newborns, and that requires operating in this general population setting.

So, right -- we've done a number of pilots already, and we've learned something interesting and different probably from all of them. The SCID pilot is done. It's actually one

where I think when we started the pilot, I think there were 25 genes known to be associated with SCID. Now, we're in the neighborhood of 50. You know, statistically it was an interesting problem because even though now we're at an incidence of about 1 in 45 to 50,000, I think we were near 800,000 babies by the time the first true positive came out of the pilot. So, it tells you how hard it is to really get a handle on how big a pilot has to be to get to an end point of being able to measure whether it's a successful pilot or not.

Pompe disease brought much more adult-onset of a higher incidence than we thought, largely because of adult-onset forms or non-penetrant forms that we had not appreciated. Mucopolysaccharidosis Type 1, X-ALD -- carriers start to fall out into the system. SMA and Duchenne muscular dystrophy -- now we're starting to get into subgroups of a disease either because we're only looking for the exon 7 deletions in the SMAs or in Duchenne because the treatments that are coming are highly targeted at narrow subgroups

of a disease population, and it begins to make you ponder what it is you're screening for.

Because if you think about a newborn screening pilot, our goal is really to -- to look at the process. We screen for something, identify those at risk, go into the diagnostic setting to figure out what they are, treat them, check the outcome, and it's that outcome that determines whether or not it justifies that being in newborn screening for the long term. So, my narrow definition of what the target is is that thing on which we understand the outcome, that is the basis of the pilot, that ultimately helps you decide whether or not its appropriate for newborn screening or not.

So, as I mentioned, this is not an ACMG talk, this is an NBSTRN talk. Several members of our Steering Committees, Sue Berry, Piero Rinaldo, Amy Brower, Bob Currier, and myself drafted a manuscript that includes most of what I'm going to talk about today. It's still working its way through the Steering Committees of NBSTRN,

which is where the authorship for the broader paper will lie. And, as I said, our problem really is understanding the measures of progress. How do we understand? There are certain things that tell you how your -- your pilot study is developing, how confident you are that whatever it is you're seeing is likely to take place in the real world. So, we've been thinking a lot about what are those kinds of measures, and there's clearly two kinds. There's those that tell you what your progress is in being confident about the results of your pilot, and there's another group that are sort of the things you get at the end, that you may end up setting some parameters around, you know, if at the end of all this you find out that you've got a positive predictive value of 1 percent, maybe that's not the best thing for newborn screening. But, as you'll see, some of those endpoints take very large numbers to get to, and how you get to those endpoints and continue to capture data and monitor things -- like we heard about homocystinuria yesterday is

going to be increasingly important.

So, we're going to talk a little bit about what's coming, what's changing, and what we've thought of as being the classical newborn screening model, and what are we going to need to deal with some of those challenges. I'm going to spare you hard-core statistics and just try to boil it down to make some examples about the size of populations that might be needed to really feel comfortable or confident in what a pilot is telling us.

And then we've already talked some yesterday about some of the capacity needs. Clearly, the newborn screening programs have capacity for workforce -- with workforce problems. People are turning over. It seemed to have contributed to some of the long turnaround time for things to be brought online in some states. So, both that and the medical genetics workforce, we'll talk a bit about.

So, from the NBSTRN side, where we're looking at these new treatments and whether or not

they're effective or not, the pipeline is really getting full of things that we had not expected to be in the pipeline. There's already a number of conditions that are candidates for newborn screening that are ready for pilot studies. If you think about how we currently fund the pilot studies, I think NICHD has been funding a pilot a year roughly, and the Advisory Committee is sufficiently resourced to do a review per year, maybe overlapping at the end of a year with a new one, and that's -- neither of those are going to be aligned well with what's coming. So, I think we do have to look at the overall model, and we certainly talked to those developing the Newborn Screening Saves Lives Act Reauthorization about what the longer-term needs look like they're going to be.

Interestingly, well, I'll come back to the kinds of conditions that are awaiting pilots. Funding is limited. The targets are changing. If you look at the pharmaceutical pipeline, there a, I mean, we're moving into a --

an era of molecularly targeted drugs, which really are the ones on which we're going to understand that outcome in patients -- a subgroup of patients with a particular disease from. We have lots and lots of off-target things hitting the workforces right now, and we haven't figured out who -- how to distribute things -- all of these late-onset forms. Is that the problem of the public health system or is it the healthcare system where the providers should be monitoring the risks that that group of patients has, even if they're not candidates immediately for the treatment. We don't know exactly when to start the treatment, perhaps. But, you know, I think it's something we're going to have to think about to take some of the pressure off the medical genetics' workforce and off the newborn screening programs is to figure out who's responsible for what.

Rare diseases are the fundamental problem we're dealing with. You know, it's -- it's not genetic disease so much as it is just rare things. When you move rare -- try to deal

with rare things at the population level, you have a significant problem of building a statistical assessment. So really, I think we have to define what are those measures of whether or not something is likely to -- to behave or perform in the real world the way it did in the pilots. You actually have a very different set of problems of measuring that performance and getting strong statistics and yet accommodating the fact that rare diseases are hard to meet certain -- they need some latitude in meeting certain requirements.

So, conditions ready for followup pilot studies already, proximal urea cycles. There's a lot of conditions actually which are already -- where the data is already available from tandem mass spectrometry. The amino acid run -- not all assays are actually refined at the low end, but there's a number of conditions with low levels of amino acids that are candidates for newborn screening, and it doesn't fit our model of funding the pilot study itself as an analytical

pilot, because really what we need for these is the long-term followup data because the data is already available in many of the runs of a tandem mass spec that are picking up this analytes already. So, we have proximal urea cycle disorders. We have remethylation disorders that are already candidates. We're running a survey right now among ACMG members and SIMD members asking them to rate a whole of probably 30 to 35 conditions for where they think we are in understanding the condition, what do we think of a particular set of biomarkers as being candidates for newborn screening types of analytes, and then -- excuse me -- and then what are these, you know, what is the treatment side of this going to look like.

So, we have a series of conditions with low valines, leucines, isoleucines and other groups that have low serines and glycines, all of which are available to us in the screens we currently run if we open them up and see everything in a profile format that is being --

that can be analyzed from some of these runs. Lots of LSDs have treatments coming and are going to be candidates for pilot studies if they're not already.

We get approached at NBSTRN by a lot of different groups interested in something that they're working on being part of newborn screening. Interestingly, there's sort of a convergence between actionability and the genome and things that people think should be part of newborn screening because they're medically actionable to the benefit of the individual. Many of these are molecularly targeted things, and I think it's an important paradigm shift to think about, you know, there's infectious diseases -- I was always surprised that Joe, with his background, didn't take on the infectious diseases because we certainly didn't when we did the Uniform Panel for Newborn Screening. But those are molecularly targeted types of analyses.

And then we have this -- all these molecular phenotypes that we're targeting in

pilots. You know, in the newborn screening world of molecular diagnostics, things with a yes/no answer where we've curated the variation of the gene and know whether it's pathogenic or not are things that are easier to move into newborn screening than is the concept of having to -- to interpret sequence variation. It takes a very different skill set and is going to be an interesting workforce issue that we'll have to sort out and figure out where do things take place in the system.

I think Sue Berry mentioned the iceberg problem, which is that we only know that little bit about these conditions before we get to the population level. The severe and the early-onset forms are really what we're targeting. Lots of subtypes we've mentioned and now, even scarier -- not scarier -- but even more -- makes you really ponder where this is going, the first reports of identifying people with molecular abnormalities at an individual level and creating a treatment for them has begun to be reported.

So, it's outside of a disease context. It's really at the molecular level that these designer kinds of treatments are coming.

So, when you think about the kinds of treatments, we already have things like chaperones -- chaperone treatments for biochemical disease. They're dependent upon having a protein there that's abnormal and can be conformed to function more normally. So, we already have some drugs where we're targeting a subset of the patients -- those that have a protein. There's a lot of -- and some of these you see in Duchenne coming now, the ability to do RNA-directed exon skipping to get through a new stop codon that didn't allow the protein to become full linked. Now, you can read-through it and get a much more normalized protein. Read-throughs are out there. Pre-mRNA splicing types of modifiers are coming pretty quickly. RNA interference is another whole set of therapeutics that are coming down the pike. I can't talk about any of these long because we're going to run out of time if I do. And then substrate reduction

therapies are coming pretty quickly as well.

So, as the targets change, we see this now -- we're doing a parent project for -- muscular dystrophy is funding a project to do a pilot for Duchenne muscular dystrophy in the state of New York. If you think about what is the target of that -- if you think about this is a condition that's maybe 1 in 5,000 -- the treatment is really an exon 51 skip or read-through to get a more normalized protein in individuals with that specific abnormality -- it's about 15 to 20 percent of the muscular dystrophy patients. It's very important for NBSTRN because if we're trying to figure out how we're measuring success, now we took something that was 1 in 5,000, and now we have 15 to 20 percent getting treated. So, the size of our pilot now has gone up significantly to be able to get enough patients who get that particular treatment to measure whether they got the outcome that we wanted to justify the decisions you have to make ultimately of including something in newborn screening or not.

Gene therapies are coming pretty fast. There's a ton of them in the pipeline. But just in the last several weeks, two of the SMA babies getting gene therapy have died -- maybe not specifically related to the treatment. It's always hard in a disease as severe as that to distinguish what was caused by the disease itself and what might be a treatment related loss. So, it's very complex and very hard in rare diseases to sort through these things. But, you know, our sense is that the primary targets are going to be those things for which we have that outcome data and everything else is going to be a more secondary or incidental-type of finding that the clinical world will have to deal with.

So, we have significant challenges with rare diseases. As I said, I think that underpins many of the problems we're having to sort through in thinking about how do we measure where we are in a pilot study. You know, incidence of disease, we find out, is very different. There are -- I don't know of a

condition that was in the Uniform Panel back in 2005 when we recommended that panel that turned out to be what we thought it was at the time. Many of them are far more common than we thought once we got to the general population. You know, we're finding that there's a lot of variability in the time of treatment and disease onset that's going to require longer-term data collection. Those are not just one-time collection during a pilot study. And, in fact, if the longer-term goal is to be able to monitor whether a condition continues to perform or not, then, you know, we're going to have to have ongoing centralized data collection.

How do we monitor these things over time is really going to be the question. And in rare diseases, the system has certainly found ways to accommodate rare diseases. If you think about the Orphan Drug Act, it recognized that, you know, these drugs would never become available to the patient population if some allowances in FDA and legislation developed a way to give a bit less

robust statistical requirements for these rare things but imposed a post-market surveillance period where you have to collect data into centralized databases typically done by the manufacturers and pharmaceutical companies who get that sort of allowance statistically. But now they have to collect data to make sure things are actually continuing to perform the way that they were thought to based on a fairly limited population.

And then, I think we're going to have to sort out curation of the genetic variation. One of the worst things we watch at NBSTRN is when a condition goes into newborn screening and we find out that variants of uncertain significance are just flowing out of the diagnostic labs, and we can certainly clean that up. And the ClinGen Project is probably prioritizing newborn screening genes in order to get them curated so that when these conditions go into more formal screening and out of pilots that we actually have a much cleaner view of what the clinical information in the geno

means when we're diagnosing.

So, I'm going to run though quickly just a couple of slides and give you a perspective on the magnitude of the problem at the population level. So, as I said, I think our goal is really to understand how likely is it that the data we're collecting in the pilot study is to perform when it gets out into routine practice. And so, what are going to be the measures of these things? You know, positive predictive value, I think, is going to be important, but that's an endpoint, and it requires a lot bigger numbers that many of the other parameters do. And we have to do all this measurement and define how we're evaluating things, but then recognize that we do have to build in some accommodations because of the rarity of many of the conditions and subgroups.

So, I'm going to show you a couple of examples. You know, our measures of what we think are those that tell us whether something is going to perform in reality as it did in a pilot are really the confidence intervals around the lower

and upper confidence intervals. You know, typically we're looking for about a 10 percent spread in confidence intervals in order to -- to feel more comfortable that it's going to pan out in the real world. And coefficient of variation is another measure of the spread of data or the standard deviation around an average, and again it's about a 10 percent -- excuse me, I am dry. So, I'm not saying that these are going to be the measures that we're going to apply but just to have sort of a starting point to look at the numbers, we'll say 10 percent CV or 10 percent confidence interval differences are the measure of whether something is going to pan out in the real world.

So, false positives. It turns out that you can accept the false positive rate with relatively low numbers. Now, all of these slides are going to have the same backdrop to them. We're talking in incidence of something that's 1 in 10,000. We're detecting every single person that has it. We have a positive predictive value

of 20 percent, so 1 in every 5 will turn out to be actual patients. And a false positive rate of 0.05 percent, which is a pretty decent performance for a newborn screening test. So, you can see that you get down to a coefficient of variation of 10 percent around 200,000. You don't even get near that -- well, these are pretty tight confidence intervals already. So, you can see that we're understanding at the level of a confidence interval pretty early what the false positive rates are looking like.

When you think about the detection rates, population sizes are very much tied to that. You can see that if we're doing 100,000 in the population, confidence intervals are pretty broad still. Once we get up to 600,000 in the population, we've got that 5 percent spread in the confidence intervals. So, just to get a sense of how big some of these pilots are when you're looking for rare things in a general population. It turns out, for positive predictive value, it needs very large numbers just to get to things

that are in that 10 percent confidence interval, 10 percent coefficient of variation range, 350,000, and this is for something that's 1 in 10,000. You get to some of the things we're doing now, which are 1 in 20 and 50 and 100,000, and these things explode.

So, now, you know, if you think about it from that -- that decreasing incidence of conditions and see what happens to the positive predictive value, it really gets killed as things get rarer and rarer, because that's a critical component of the calculation of positive predictive value as the incidence of the condition. And I think you're probably going to have to think about whether you draw lines or prespecify that something -- you need to be around perhaps 20 percent positive predictive value to take it into the general population. If you start getting much beyond 1 in 10, 1 in 5, then you're going to be alarming an awful lot of people to find that 1, and a lot of things will go into that decision. But it's going to be a difficult

problem.

Now, the false positive rate actually can manage that problem if you stay around a positive predictive value of 20 percent. Then you can see that the false positive rate -- in order to maintain a positive predictive value of 20 percent, the false positive rates have to really start dropping precipitously to maintain that performance. So, I think -- thinking a lot about that, the mechanism by which we control false positives is going to be critically important and, you know, we've certainly seen things like the CLIR tools as a mechanism of trying to develop ratios and other things that get us a higher likelihood that if somebody is truly affected out of a newborn screen, there are second-tier biochemical tests that can be very informative. In many cases, we use that right now already in -- in CF, where, you know, many go from IRT to IRT to avoid all the carriers that come out of a DNA component of a second-tier test. So, second-tier biochemical tests can perform very well and, I

think, are something we're going to have to pay close attention to as to whether then can both manage some of the workforce problems of off-target things getting put out into the diagnostic setting and give us a higher positive predictive value for those individuals screening positively.

As I said, workforces are seriously misaligned right now. We had a -- we were fortunate in that Congresswoman Herrera Beutler put into the Labor HHS 2019 Appropriations a Medical Genetics Workforce Study because it's already being recognized that for what's coming in non-invasive prenatal screening and newborn screening that we don't have the workforce that's going to be able to deal with this, and newborn screening programs have the same problem with their staffing as more new technologies come in, more work on the clinical end of interpreting is coming into their programs, and that whole area of complexity is showing that the analytical parameters are becoming very different than the clinical parameters. You know, we can do

analytical validation regardless of whether you're a late-onset, non-penetrant, early-onset, it's finding the target. Once you get to the clinical validation side, now you've got a subset of the group in whom you're measuring outcome, and you have quite variable diseases so that, you know, it's very difficult to go from one patient or two patients with a particular condition that could be very different than, you know, other patients with the same condition.

So, how are we going to deal with this -- this increasing capacity demand? There's a lot of conditions already ready for pilot studies, a lot of new treatments in the pipeline that change the way we think about what the targets of screening are going to be. So, I've already mentioned, you know, thinking about some of the off-target results, whose problems are they? If we want to open up capacity in the newborn screening laboratories, then they're going to have to rely upon the clinical world, and that's difficult given the tenuous nature of our

electronic health record systems in the country, because that's really where you want to be able to maintain things like carrier status that could be used much later in life. You know, so we have to make sure that our workforces are going to be aligned with this coming demand. We need to think about a system in which the very limited data that's available for screening for these can be developed in a controlled and organized way, and because they're rare, I think that does mean the centralized data systems or at least highly compatible data within different data collection systems. And then, think about the alternative financing models, because this is a much broader range of stakeholders. A lot of these same problems are happening across genomics. They happen in the world of getting things into developing countries, and how do you resource that? And public private partnerships have been developing worldwide to deal with some of these really rapidly moving areas of science where your, you know, your capacity to take on what is in this

pipeline is very limited, and there are lots of interest groups beyond just the government and thinking about some of those models is going to be increasingly important.

You know, we're going to have to figure out the regulatory side. There are model systems for ensuring that rare disease treatments are developed and made available, incentives to the pharmaceutical industry to develop those rare disease drugs. We have a different problem on the diagnostic side, but there's no reason that the same problem, which is rare things on a diagnostic side instead of a treatment side, need some latitude in the system for being able to move forward or else, you know, we have it for the drug side. If we can't identify the patients who are going to benefit from having access to that drug before they're clinically affected, then we're going to really limit the value of those drugs over the longer term. And the Orphan Drug Act has accommodated that, and I think there could be models. FDA already has a mechanism of

provisional approval that allows for certain things to be met before it goes to full approval. So, there are systems in place already by which some of these things can be addressed.

We'll have to look at reimbursement systems. You know, typically if you think about coverage with evidence development that is a CMS model, or how do you sort of incentivize people to make their data available to understand what the answers to a particular problem are, you know, coverage with evidence development does that. But it happens on a much tighter scale, typically, than our problem is going to accommodate. But the first problem is, what don't you get paid for today that would be an incentive? So, cycasin, for instance, for Krabbe -- providers can get paid for cycasin testing because it's done in asymptomatic individuals to determine whether or not they're likely to be preclinical or in the early stages of clinical presentation.

So, thinking about how do we fit together some of these various models we have of

coverage with evidence development, sort of provisional approval, and then a much broader range of stakeholders to enhance capacity, and certainly to minimize duplication of effort of things that might take place in newborn screening programs as compared to the diagnostic clinical world.

So, public funding is limited. I mentioned how much is available now for this committee's review work and for -- to support pilot studies. You know, we're going to really need the centralized data sharing until we have really robust EHRs that do something more than just the business side of medicine. Interesting, public private partnership models, you know, I've mentioned some of the risk sharing, which is a number of pharmaceutical companies contributed funds to PPMD to support a pilot study in New York. It may be a pilot study that fails, but it's a risk-sharing model. They were willing to invest in it to see whether or not that said we should be screening for this group of patients

with Duchenne muscular dystrophy. We have patient-drive data sharing. That works up to a point, and it's what we often think about in developing registries. But, there's very different incentives for clinically affected people to share data than there are for asymptomatic people. They are pretty unmanageable folks on the asymptomatic side. They don't have the same incentives to bring all their data into these systems, and they're the hard group for us to begin sorting out.

You have managed-entry agreements in Europe. There are ways by which they're making decisions about oncology drugs and what should be -- how it should be priced, how it should be reimbursed and fit into their systems.

So, if nothing else, there's a lot of problems coming. I think you've already started talking about what are the -- the targets of newborn screening, you know, and that's going to be one of the first ones, because I think it translates all the way back into the pilot studies

we run, because we have to be able to measure where we are in the course of a pilot to getting us the answers we want, and that's a challenge for Cindy now, I guess. All right. Thank you.

DR. JOSEPH BOCCHINI: Michael, thank you very much. And thank you for the understatement of the day that problems are coming. All right. This presentation is open for discussion, questions, and comments. Let's open it to the committee first.

DR. MELISSA PARISI: Melissa Parisi, NICHD. So, Mike, thank you for that presentation. I thought it might be helpful for this committee and group to know a little bit more about the work of ClinGen in particular with regard to the Inborn Errors Working Group, the Expert Curation Panel, and the fact that the determinations for molecular variants that are identified now have FDA determination and weight to them such that they can be used by newborn screening programs when molecular testing is a part of their screening algorithms.

DR. MICHAEL WATSON: Yep. So, I -- I'm one of the co-PIs in the ClinGen -- the Clinical Genetics Genomics Resource Initiative, which is all about clinically curating the magnitude of gene relations to disease and determining the pathogenicity of variants within the genes that are parts of tests. You know, it's an interesting problem, and from a newborn screening perspective, I think the mendelian disorders, you know, where you know that gene and it's pretty well validated have been pretty straightforward. Our problems come in the phenotype-driven kinds of screens like T-REx assays where now we have 50 genes. There have been publications over the last probably six months showing that what we thought here genes that should be screened are sometimes awful -- have very weak associations with diseases. For hypertrophic cardiomyopathy, there were like 35 genes being tested in labs all over the country. After curation, it turned out 8 were strongly associated with hypertrophic cardiomyopathy, 3

more moderately well associated, and whole bunch went away. Same thing with Brugada syndrome, where a whole bunch -- it was like 22 genes being tested in most laboratories for people at risk for Brugada or who presented with Brugada syndrome. One gene turned out to be strongly associated. All the others were sort of things that had biological plausibility or other fairly weak associations with the disease itself. So, I think our office -- Meredith Weaver in my office -- coordinates the metabolic disease workgroups, and we are prioritizing all the newborn screening genes associated with metabolic diseases in order to hopefully clean up that first stage of diagnostic followup that takes place after the screening takes place. But I do think that getting that curation -- and we're working with partners. We're talking to groups that have interest in specific diseases and genes to see whether or not they're interested in getting involved in curating those and getting them cleaned up before they get out into practice.

DR. MELISSA PARISI: And can you say something about the FDA determination in January?

DR. MICHAEL WATSON: Yeah. So, that is -- that's actually -- for rare diseases, that's really an enormous value that FDA will recognize the ClinGen-curated parts of the ClinVar database that NIH maintains as being the clinical validity of how you're going to call out a variant as being benign, uncertain, or pathogenic. You know, I think that's partly why we have laboratory developed tests in the United States was there was never a way for a pharmaceutical company or for a devices company to develop a test for a rare thing and ever get a return on its investment for that when it's tested in so few people when it's a really rare condition, and that led labs to develop laboratory developed tests, because there was no return on investment for the industry side that would have developed those tests and sold them as kits to laboratories. So, it's a problem, you know, that is really because of the rarity. Genomics may change that. We'll have to wait and

see. But, yeah, I think having FDA having recognized that certainly makes it easy for every lab in the country now to say -- to meet the requirements for what are you going to do with the results that come out of your machine, because it basically says, this is the clinical validity database, and I'm going to call it as that database defines that particular variant. So it -- it really lowers that bar on that clinical trial expense that comes for finding rare things in the population and allowing labs to have the kind of data they need to have more accurate diagnostic reports and -- and even in the screening environment when those become the second-tier tests.

DR. JOSEPH BOCCHINI: Kellie.

DR. KELLIE KELM: Kellie Kelm. And I just wanted to clarify that the recognition only supports the use of that database for FDA pre-market submission. So, how other people want to take that recognition and use it, that's up to them. But FDA's recognition was for its use in

FDA submissions -- excuse me -- only.

And I did want to comment about your -- you talked about there being some other process like orphan drugs for tests, and we actually do have a humanitarian device exemption program for high-risk things where the numbers -- and I forget, they changed under legislation years ago -- it was under -- it was like 8,000 people per year. So, the process, though, you have to show safety and probable benefit, which is lower bar, but the problem is that you can only recoup the money that would be for R&D. You're not allowed to actually profit. So, I mean, that's how Congress set it up. It's not something that, you know, I think a lot of people dislike the fact that you can't -- that there's limits on the program.

MR. MICHAEL WATSON: Yeah.

DR. KELLIE KELM: But, you know, that is what it is, and screening -- the difference there is the fact that you're testing so many kids that, you know, you obviously need to -- it's not

only being used on a small number of kids. But, you know, most of the studies that we see for those submissions are the kinds of exact studies that I know the states are already doing, and in many cases are, you know, small retrospective studies. And so, you know, something to keep in mind.

MR. MICHAEL WATSON: Yeah. No, I do keep it in mind because I, you know, it's in Congress' hands right now with the VALID Act that is being drafted -- the discussion drafts a VALID route now, which is essentially going to make LTDs and in-vitro clinical tests and bring the labs in as manufacturers essentially under some level of regulatory oversight. We'll see how it goes. It's had difficulties in the past getting through. But right now, they seem to be better aligned than they have in the past about how we're going to try to get control of the laboratory side of some of this.

DR. JOSEPH BOCCHINI: Carla.

DR. CARLA CUTHBERT: All right.

Thank you for that talk. I have a quick question. I think I understand that a multiplex pilot study would be, but what's a virtual pilot?

DR. MICHAEL WATSON: A virtual pilot -- so that basically says that we already have a bunch of, I mean, a lot of this data is already available. It's a matter, you know, if a lab ran a full tandem aspect profile of the aminos, then they know which people had low leucine -- isoleucine or low valines or low cerein. Now, what we need is the clinical data about those individuals and, you know, that's a difficult problem in the public health world that doesn't always want to be sort of aligned with the perception of doing research. And, you know, clearly, we are -- we're going to -- it's a model that's been used sort of peripherally in the past where we go out and find providers who are taking care of certain types of patients. We then ask those patients -- and this has happened in many of the early-stage pilots -- once you identify those people, find their blood spot, you can now ask the

question of whether you could have detected them in a newborn screening blood spot or not. But the virtual pilot says that we have some of the data already available and now just need a piece of it and, you know, most of the followup side has been sort of relegated to the reimbursement side of health care rather than being a funded kind of study.

DR. CARLA CUTHBERT: So, is that instead of being a prospective it's looking back retrospectively to look at all of the pieces?

DR. MICHAEL WATSON: Yeah. In fact, California and Mayo and others have already pilots for some of these. So, it's a matter of capturing the data from the pilots they already ran that are what allowed them to make decisions about including it on an ongoing basis in their screening programs.

DR. CARLA CUTHBERT: But these children would not have been identified, I mean, I'm just trying to understand. These kids would be identified clinically, would not have been

captured within an early newborn time point, and so the benefits may not be the same, right? Is that --

DR. MICHAEL WATSON: Yeah, I mean --

DR. SUSAN BERRY: I can give an example. Would it be helpful to have an example?

DR. SUSAN BERRY: Yeah, so, for example, in Minnesota when Mayo was running the MS/MS part, they -- routinely when they found low methionine would pursue that and then share that information with us, even though it wasn't on the pilot because the way our statute was set up is they had things that were on the screen, but if they found something of significance, they would pass it on. We picked up children with cobalamin G, for example, with low methionine because they found it and they called it out, even though it wasn't formally part of the screen. And so, for many years, that was part of one of the things that happened for us. The same thing was true for low citrulline.

DR. MICHAEL WATSON: And you see

variations on that and, you know, when you look at Washington State and the way it does its pilot studies, which are fully anonymized, for many of the LSDs. You know, these are rare things. They may find something and say okay, somebody in this anonymized group is going to have this disease and then they're waiting for that person to present for care later and, you know, but a lot of these variants are very rare. So, when the person comes in and you find the variant, you know they are actually one of the anonymized people from your pilot study, and that's not, you know, that's a difficult model, I think, when the public says somebody knew, you know, before becoming clinically affected, and yeah. So, addressing some of these -- these kinds of problems, I think, is going to be important to the sort of next paradigm shift in newborn screening.

DR. SCOTT SHONE: Scott Shone. Sue, to your example, though, I was sort of tracing with Carla. I don't think it's the same thing, because what you're saying is that -- that

cobalamin G was perspective identified -- it was picked up off panel. But, again, the child went through diagnostic workup and followup. What I think -- what, Mike, you were saying in terms of a virtual pilot is going back and reanalyzing data and then what you just said is perhaps because it's rare, you can eventually link that, and Mike Gelb talked about that in some of what they've been doing in Washington.

DR. MICHAEL WATSON: Yep.

DR. SCOTT SHONE: But I want to get back --

DR. MICHAEL WATSON: Our goal is to get the data, right? And if the data already exists, then how do we bring it together so, like any other pilot, we're able to look at it and make decisions about whether or not it was appropriate -- it might be appropriate as a target of screening.

DR. SCOTT SHONE: So, I agree with that, and I think that that gives us one piece, and we've had this policy discussion many times.

In the briefing book was the report that came out of the Pilot Studies Workgroup from a couple of years ago. But I still think that in the scope of the pilot study discussion, we need -- I just want to make sure we're on the same page that there still needs to be this system -- this system-based perspective pilot study that assesses that every piece of the newborn screening system is going to work together to effectively, accurately identify a child with a condition, that while each of these examples are sort of just like subgroups of disorders that are now being targeted, subgroups of an all-encompassing pilot study, there is a need to ensure that the scope of the pilot study that is used as part of the evidence review is all encompassing and that we have a -- we can have -- it's not just cherry picking this and then putting it together in the end, and I realize that's a high bar. But I do think that high bar is critical for this group.

DR. MICHAEL WATSON: Yeah, I do too. You know, I do think it's going to -- it's like

the five-of-a-kind model that FDA uses, you know. As you bring more neuromuscular diseases into newborn screening, you will have already identified your provider of population that they're going to go out. So, every new one that comes in isn't going to require the same system issues of sort of defining, you know, everybody that's needed to ensure the care of that individual. I thought you were going --

DR. SCOTT SHONE: No. Just to add -- but I have a separate question, though. So, I agree that in the scope of -- so, with what Alex was talking about yesterday with the evidence review and sort of the multiplex pilot, juggled two things in my mind. One is sort of like what Melissa is proposing to do with a whole host of different disorders or multiple subtypes of say the class of disorders. And so, how -- do you have -- have you thought about in the scope of what's going to come out of these pilot studies, how the evidence review is going to work to look at that kind of thing.

DR. MICHAEL WATSON: Well, I've thought about it and, you know, I don't know the answer necessarily, because there's lots of parameters around what you might multiplex. You know, you can multiplex around the testing platform so that if you're, you know, in tandem mass spectrometry, you could do everything in a pilot of tandem mass spec. You could run the pilot around the specialty providers who deal with that patient population. So, there's different ways you might develop, you know, some of these multiplexed or groups of things around how you -- if you're multiplexing and the question is all about the clinical outcome, then multiplexing things that are going to the same set of providers is one possibility, having it on the analytical end is another, you know, is another possibility. But there's so many, I think, that doing all the -- and, in fact, if -- if the LSDs do inform each other as to, you know, as to what the analytical validity of a result might be, then running them actually may have value as well -- running them as

a multiplex in a pilot.

DR. JOSEPH BOCCHINI: So, I'm going to open this up to the organization representatives and those on the phone if there's one quick question. Debra.

DR. DEBRA FREEDENBERG: So, I'm certain you can really answer this, but given the number of conditions that are waiting in the wings and pilots are starting, and the clinical workforce shortage, as well as both newborn screening program workforce shortages, and competing priorities, do you have any vision of how this is all going to translate?

DR. MICHAEL WATSON: No. Sadly, you know, I do think it's the -- it's the -- it's a system problem of how you fit it all together and how you finance it. That's why I do think that other models then just expecting the federal government to be, you know, the major contributor. The state governments already contribute a fair bit with -- through their newborn screening laboratories. You know, we have other

stakeholders. The Mayo -- even though it has a patent on the CLIR risk analysis tools -- has exempted it from all patent enforcement when used in the area of newborn screening. So, that becomes part of a public private partnership contribution to managing some of these problems.

But, you know, it's -- it's this rare thing in the big population that we have to deal with. I think it's going to take getting that data started at the pilot study stage, continuing that in a post-market surveillance environment so that we continue to make sure that the test is performing as we thought it would. And then, if you ultimately want to get to the point where you're able to monitor as a committee whether or not, you know, something is doing what you expected, then you're going to have to have that same kind of data. So, you know, I think a centralized data-kind of system or at least compatible data that's in different systems is going to be important to a number of steps of ensuring that the performance of these screens is

doing what we had thought it would.

DR. JOSEPH BOCCHINI: All right. Michael, thank you very much for this thoughtful presentation. I think that the same parameters could be considered for -- as we look forward to the potential of looking at conditions that are already on the RUSP to apply some of these same principles to evaluate test performance and -- and understand what we're really identified. So, thank you.

All right. Next on the agenda is a presentation by Dr. Baker. Mei is the head of the -- the Chair of the Ad-hoc Workgroup focused on interpreting newborn screening results and has an update for the full committee. Mei.

AD-HOC WORKGROUP - INTERPRETING NBS RESULTS

DR. MEI BAKER: Good morning, everybody. Before I start, the one thing I want everybody to know, especially committee members, we have some modification in terms of charges. If you recall last meeting on March 27th -- this was through the webinar -- we were in charge in two

charges. One is titled here and is Interpretation of Newborn Screening Results and also, we've been asked to address cut-off to see if we can come up with some recommendations. And yesterday morning, we met, and we -- it's a consensus from the whole group for two reasons that we did some modifications. The first thing is when we discussed the first charge, since things are getting more and more complicated very quickly and the world needs our attention. And second part is the two charges put together to discuss sometimes among ourselves can get maybe a little bit confused. So, we want -- we also think the second charge is such an important topic, we think it needs our full attention. So, we're going to table this aside for the time moment and then address it later. So, now it's everything regarding previously charge one.

So, this is our group. I hope it's well represented in most disciplines and I want to emphasize a new member, Kyle Brothers, new-coming member in the Ad-Hoc Group, so welcome.

In terms of how we address, we set up the charge forward. This is what we call our method of approach. First, we create a report to the committee and also, based on the report, hope to generate some publication, and the third one is to create some education material. So, we talk about work trend and dissemination. So, this is kind of embedded in that because trying to get a publication, trying to create some slide stack, it's for dissemination purpose.

So, how we envision this report structure, and this is not new to you, but I'm just trying to put it together and emphasize. So, we have three parts. Part one is introduction. Part two is address or describe the current practice. The third one is the discussion and we hope naturally comments, suggestions, or recommendations.

So, what do we want to accomplish in the part one? So, this is the thing has been evolved, and our purpose yesterday morning was trying to say do we include everything we want to

address. So, I hope committee members and audience members can help us. That's two slides, just so you know. First, we want to address rationale, and then, you know, going to the literature search. I think we're not alone, and come to the medical screening, indeed sometimes I think the emphasis is on benefit. We don't talk about limitations and we put it in the position that it's created this -- this, you know, unrealistic expectation. So, I use the words trying to be more neutral, so we think of transparency in terms of benefit and limitation. It's important.

So, the second part of each line is really indicative of the target audience. So, we want to target the health organization and also our parents and public. So, that's just a general thing. And other things that we did a lot of discussion is terminology, because this is a very, very sensitive topic. People use harmonization, talk about standardization. So, for the time being, we want to use a consistent -- this is

stated in the literature. So, I think again, we're not alone. I think it's important, and we hope we come to some consensus.

And the second part we want to address, it's the knowledge gap and also what's -- really point out what's our attainable expectations? So, screening, coming to the diagnosis that we will address further. So, there's a list here. I don't think anything is new from last committee meeting.

So, another thing we want to address is to go to a more deeper concept of newborn screening, population screening, diagnosis, and then it would come to the testing. And actually, you can find it in a literature search, and somebody that has done some work, most are familiar with Region 4, come to this material have a table to compare with, so the tests are different and also have APHL QA committee also to talk about what's the screening entail.

So, I think in those things, we want to be sure, no matter what you do, no matter where

you cut, to always have exceptional. People need to realize that. If anything happens, you change your whole system, and that's not the only way to address the issues. So, we need to state this, and people understand that.

So, part two. So, what is the current practice? So, we want to collect the data and understand how we do that. I do believe from my heart -- and I know that because I believe it every day -- it really is screening in mind. But I think we can just describe certain evidence, so the public understands. And I think the key thing here is threshold based. Also, we do the categorical, I mean, categorize what we do. So, this is very different mindset than currently, and also, I do believe every single case -- screening part of the case -- we already say please do the clinical confirmatory test -- do the clinical assessment. So, this is an important concept.

And again, continuing we talk about the report, and I think hopefully it's inclusive of everything and that, you know, at our meeting

yesterday, we talked again about two screenings. So, we'll maybe even address it a little bit more in the discussion portion.

Part three is a discussion -- it's where we think we need to do more risk assessment more clear so people understand what it is. Another thing I feel what we are doing now, and actually I've been asked questions, if like other entities are doing similar things, why do this. I think the one thing that sets us apart is we perhaps intentionally use the newborn screening report as a vehicle constantly every single time as a reminder of our primary care physician. We will have an interpretation for normal newborn screening or screening negative results indicating that even this is negative, but the clinical symptoms take a precedent. You do need to assess that. So, every single time instead of reading the material, it's like every single report is a constant reminder. We hope this will be more effective. Again, we will address the terminology, the clarification, and consistency,

and we hope we can come forward with a strategy for the communication. I think for this part, we must rely on the work that has been done by education subcommittee. They have some material. We hope that we can further disseminate this work. And I think this is the most part, and we will use it to address and improve the newborn screening. So, we make this risk assessment better for whatever.

So, that is the revised timeline, and it largely stays the same. We hope we are still on track. And one thing I want to mention that we didn't spend much time talking about dissemination, but the concept is still here. Since I haven't mentioned that, it is a potentially to do the professional conference to give presentations, also through our other organizations to disseminate what have we learned. Fortunately, in our group, we have a lot, I mean, other organization groups will help us to do such. Thank you.

DR. JOSEPH BOCCHINI: Mei, thank you

very much for that thorough report. I think we're going to now just ask that the committee members and org reps and others who have input that they want to give to Mei or the workgroup to go ahead and do that directly or through HRSA so that they can give feedback on the process which I think is going very nicely. And I want to thank the workgroup. It think the representation on it is very strong, and I think having the laboratory standards and the education and training workgroups represented on this committee will sort of help to organize some of the things that Mei is talking about in terms of providing educational opportunities and for providers as well as for the public. So, thank you, Mei, for your work. I appreciate it.

So, next on the agenda is a discussion or presentation about two registries. At our March webinar meeting, we heard about federal and national level research resources for rare diseases, and at this meeting we want to bring -- to begin to hear from rare disease

registries the data that's collected and the research efforts that are made for conditions currently on the RUSP. We anticipate continuing to hear from the field about research and data resources for rare disorders at future meetings as well. Our goal is to determine the role these registries might play in providing data for evidence reviews as well as to state for long-term followup.

So, first we're please to have Dr. Bruce Marshall here with us to talk about the Cystic Fibrosis Registry. Dr. Marshall is Senior Vice President for Clinical Affairs at the Cystic Fibrosis Foundation. He joined the organism -- organization -- I'm starting to sound like Dr. Kemper. He joined the organization in 2002 and directs the clinically related activities of the foundation including the Care Center Network, Quality Improvement, Clinical Practice Guidelines, Patient Registry, and Educational Resources. Dr. Marshall was a faculty member at the University of Utah School of Medicine, where he served as the

Founding Director of the Adult CF Program, a role that he played from 1989 to 2002. So, Dr. Marshall, we welcome you to the meeting. Thank you.

CYSTIS FIBROSIS REGISTRY

DR. BRUCE MARSHALL: Thank you. Thanks very much. Appreciate the invitation to share our experience at the CF Foundation. First, a confession. I'm an internist and pulmonologist. I don't know very much about newborn screening, but I've learned a little bit since joining the foundation because it's such an important aspect of what we want to do, which is intervene early and prevent complications. So, I've learned a little bit.

So, we're based just a few stops down the Red Line in Bethesda, so it's a pleasure to come up to this part of Montgomery County. I'll let you read through my disclosures; business relationships related to the registry for the conduct of post-approval research studies. This is what I'd like to do over the next 15 minutes or

so and then leave plenty of time if there are questions. Just to provide a little bit of context for those of you not as familiar with cystic fibrosis, go over the basics of our patient registry and how the registry data is used. A little bit about the intersection of the registry and newborn screening and then hopefully time for Q&A.

So, you're all probably familiar with this -- autosomal recessive disease. About 35,000 people in the US, about 100,000 worldwide, most common life-shortening inherited disease of Caucasians. It's a complex, multisystem disease with a majority of deaths due to chronic lung disease. And I'm not going to go through this slide in detail, but it goes through the multi-system nature of this disease with chronic sinusitis, airways disease that result in bronchiectasis. A minority of patients have had a biliary disease, pancreatic insufficiency, exocrine insufficiency, and about 85 to 90 percent of the population with milder genotypes. Sweat

chloride still an important diagnostic test, elevated sweat chlorides, and in males, obstructive azoospermia. And there are different flavors of cystic fibrosis. Those with a severe genotype to the left -- depicted to the left, and those with sort of a milder genotype depicted to the right with one of the major differentiating is they have typically adequate pancreatic function.

There are other important co-morbidities. As this population ages, we're seeing new things. CF-related diabetes is highly prevalent in adolescents and adults, anxiety, depression, other psychosocial issues, allergic bronchopulmonary aspergillosis, non-tuberculous mycobacteria. These resistant types of infections and allergic responses are significant problems.

As you know, there have been major advances in cystic fibrosis, and many of them track back to the discovery of the gene. This goes back to 1989, in fact is when I joined CF Care and Research at the University of Utah. And this is one of my favorite figures. This is a

young man looking back -- he's about 20 years of age, looking back at a picture of himself on the cover of Science Magazine, and this is where the major mutation in the gene was described.

So, again, just to provide some context, the foundation -- we have broad scope of activities from the most basic research all the way through to a direct contact with people with CF and everything in between. And this is the space that most of my activities -- most of my effort is focused, around our Care Center Network. There's a peer accreditation system that's been in place for many years. The patient registry that I'm going to talk a little bit more about. Quality improvement that we've pushed hard on over the last 15 years or so. Clinical practice guidelines to set a framework for care in CF.

So, just a little history about the patient registry, it takes back to the '60s -- the late '60s. It was started by Dr. Warren Warwick at the University of Minnesota based on a grant from the foundation, sort of a paltry sum of

money. But he was able to start -- start a registry and carried it forward for a number of years until the -- the early to mid '80s. Dr. Bell -- Bob Bell -- sort of an icon in our community assumed the registry -- subsumed it within the CF Foundation, and we've operated it ever since.

And I won't go through all of the milestones here other than a personal reflection. Again, back when I was at the University of Utah, I remember completing all the data and sending it on floppy disks. Some of you may remember those floppy disks. And then the modern era of the registry really started in 2003, and that's when we launched the web-based platform. It was a custom-built application and then we were -- it had some limitations. We replaced that in 2010 with another web-based application that had additional functionality. And then just this final milestone that I'll mention -- I'll talk a little bit more about this when I talk about the uses of the patient registry. Just in 2017, we

launched a web-based application that we refer to as CF Smart Reports. It's to facilitate improvements in care.

So, we've deployed the registry as an IRB-approved, patient-consented observational study across all of our care centers. This is a requirement. To be an accredited center, you must participate in the registry. Of course, not all patients consent. We estimate about 5 percent do not offer consent and participate in the registry.

We collect a great deal of information, and again, I won't -- I don't expect you to read this slide. It's just a reminder to me. We collect information about diagnosis, demographics, the care delivered, treatments, measurements in screening tests, other conditions, and events. And these are scattered across several case report forms.

Data is entered by the care centers, and we incentivize this by supporting the users, and we provide some financial support to all of our care centers, and it's primarily driven by the

number of patients that they enter data on and the completeness of that data. And we use the data for multiple purposes. I'll come back to that.

The quality of the data is facilitated by edit checks within the data entry fields themselves. If a data entry person tries to go outside those limits, it's not allowed, or they have to go and request an exception. Data entry guidelines that are widely available, we validate key metrics. For example, at the end of every year, we go back to every center and validate the deaths, ask if there are any that have been forgotten, et cetera, as well as transplants, another important metric for us. We go through an annual processing of the data, in particular, de-duplication. Our patients tend to move around, you know, when they graduate, and they go to college. They may move to another city. So, we don't want duplicate records entering the system. And then we spend time with the people that enter the data. Every year, we have a conference, and we meet with them right

before the conference for a half-day session and thank them for all they do and educate them on changes and where we've seen some idiosyncrasies in the data that we think may relate to the data entry process. So, we're constantly trying to improve the quality of the data.

We also do selective, mostly random audits, but if we suspect through a review of the data that there are some concerns about a particular center, then they'll be a for-cause audit, and we'll go in and we don't sample every data element. We pick and choose the most important data elements, and we look at those and compare to the source document -- the electronic medical records. And this has been -- the most important thing we've found with this is the informed consent process is a little sloppy. And this is run primarily by clinically oriented people and not clinical research people, so we've really worked hard to sort of police that up through our accreditation process. But otherwise, the data is, for the most part, very complete and

quite accurate.

We used the registry data in multiple ways, and we consider it one of our crown jewels. We use it -- the primary purpose when it was formed by Dr. Warwick many years ago was just to track at a national level the natural history of the disease and the impact of therapies that were being delivered. All the way to the left, you might call it disease surveillance. It's an important framework for clinical trials in terms of assessing feasibility, number of events that might be studied in a clinical trial. I mentioned post-marketing studies. This is something that we added about ten years ago, built this business on top of our registry, and it's been an important revenue stream. We've used it extensively to drive improvement in care. The main reason I joined the foundation was quality improvement to try to drive improvement and then for research purposes.

Just to give you some examples of the reports that we generate on an annual basis, we

generate a highlights report. This is typically two to four pages with various icons, catch the eye, something that somebody could post on social media to get, you know, to get attention to the registry, and it's just, you know, as the title indicates, just top-line highlights, and then a very detailed annual data report that we post online and we distribute to all our care centers, widely available. It's 80 or 90 pages long. It's paradise for nerds. They love -- like me -- I love developing this report and disseminating it.

And then, each center gets their own report. So, these are the important metrics that we send back to each center showing where they stand with respect to a process and outcome measure, vis a vis their peers and trends over time.

I mentioned CF Smart Reports earlier, and this is a new use of the registry data just in the last couple years. And the idea is we worked to get the registry data more quickly. We encouraged our care centers to enter the data.

We've worked out a process with our vendor -- we use a vendor to collect the data, to bring that data on a nightly basis into our data warehouse, do some limited processing, get that back out into CF Smart Reports in a timely way so the care centers can use this data. It used to be a one-year process, and we still go through this rigorous one-year process for the annual reports that I mentioned, but now we can do this -- if the data gets in -- if the care centers can get the data in -- we can -- we can have it in the data warehouse and out in CF Smart Reports within 24 hours. So, this is an important advance for us.

And what we've included in this CF Smart Reports -- and I won't go through this in detail -- but one of the reports that our care centers really enjoy and download extensively are these patient summary reports, and they show graphical trends on key metrics. And then to the left, that panel displays some of the key information that may not be easily readily available in the electronic medical record, like

their genotype. That's not readily handled in the EMRs. We track hospitalizations and home IVs, overlay that with trends in pulmonary function. And there's much more in the long report that's actually four pages. But most of our centers prefer the one-page version of this.

One of the ways that we've encouraged them to use this is pre-visit planning. And those of you familiar with the quality improvement space will recognize Ed Wagner's name. He developed the chronic care model. And one of the powerful change ideas that he's promoted is this idea of pre-visit planning, bringing the care team together before the visits to go over the data and plan for what's, you know, what's to happen at that clinic visit. And our care centers use these patient summary reports to help them prepare.

The other thing that we've built into CF Smart Reports is a tool to identify subjects -- patients that might be eligible subjects for clinical trials. So, if there's a new clinical trial that's being deployed, we work with our

clinical research center to get the inclusion/exclusion criteria, we built a query, we deploy it in CF Smart Reports, announce it to the community, and then if they're screening -- if their center is selected for that study to participate, they can go and just click on a button for that clinical trial, and it will display the names of folks that at least by the criteria that we have available to us may be eligible for that clinical trial. Our research coordinators really love this tool.

I thought I'd just give you one example of -- all the way too -- actually in the middle -- a way that we use the registry for research, and it's just a research line that I've been involved in, so I'm very familiar with it. And this is in regard to what is referred to as a pulmonary exacerbation, and this sort of depicts it -- the status on the y-axis is better toward the top and worse toward the bottom. This is -- this happens to be a measure of pulmonary function. It's relatively stable. The blue line

depicts signs and symptoms. The yellow line measures pulmonary function, and there's a flareup of the disease. Both symptoms and FEV1 deteriorate, and then there's an intervention, and it comes back up to baseline in an ideal world.

Why are these events important? Well, the events that require more aggressive intervention like a course of intravenous antibiotics, they're very common events. And this is data from -- from our registry. And the gray lines in the background are all the subjects in the registry at various -- various age groups in one-year increments. And you can -- you can see the drop-off as you get into the 30s and 40s, meaning life expectancy now in the mid-40s. And then in red is depicted the individuals in the various ages that experienced two or more exacerbations and blue those that have experienced one or more exacerbation, and these are IV antibiotic-treated exacerbations. So, very common event, major driver of cost. A lot of this care happens in the hospital and has a negative impact

on quality of life, and it's associated with decreased survival. And I'll show you just as a slide that again, I don't expect you to read this slide, but it's some work that I was involved in when I was at the University of Utah using the registry to develop survivorship models. And one of the things that we discovered was that each IV-treated exacerbation had an unexpectedly large negative impact on survival -- the equivalent of a 12 percent drop in FEV1, which is a pretty significant drop. So, that has -- that and other research has triggered additional research on these pulmonary exacerbations. And again, this is relevant to the registry.

We had had guidelines -- clinical practice guidelines in development, and the committee suggested that we needed more research, that most of the recommendations were consensus driven -- very little research on this -- these really important events. So, we conducted a registry embedded observational study to assess feasibility, and there were a few other aims, and

they're listed here. It was referred to as the STOP trial. We wanted to expand the capability of the registry, and we found that the registry was able -- we were able to conduct observational studies within -- embedded within the registry. We wanted to establish equipoise for future interventional trials, and we found that yes, this -- the center staff felt like for some designs they would be at equipoise and willing to participate. We used the data from this STOP study to inform future research by establishing variants for key outcome measures, and then we reached out to a number of centers, and they expressed an interest in further research in this area.

So, we've gone on -- we've conducted surveys of clinicians and patients and families to help us design a randomized control trial called STOP2, and this is one of the largest trials that we've ever sponsored. I think by the time we complete enrollment, there will be about 1,000 subjects scattered across about 50 or 60 centers,

and it's aimed at trying to determine the optimal duration of treatment. All of this tracks back to the registry.

Now, I wanted to talk a little bit, and I'm a little nervous about talking about this because I don't have expertise, so don't ask me any tough questions here. But I wanted to talk a little bit about the intersection of the registry in newborn screening. We've use it to assess what you might call performance of newborn screening, in particular false negatives, to track the time from birth to entry into one of our care centers, and we used this data for process improvement, feeding that back to states and care centers to help drive improvements, and I'll show you a little data on that.

And then, for clinical followup of those that are in this ambiguous category I'll refer to as CF-SPID, CF screen-positive indeterminate diagnosis, and I'll show you some data on that as well.

So, here's some newborn screening

metrics that I'll share with you, and there's two time periods here. 2010 to 2012, newborn screening was universally adopted in all 50 states by 2010. You can see the median age as what's referred to first care center event. That could be a sweat test, a clinic visit, et cetera, where it looks like there's been a significant contact with a center. You can see there's been a significant -- a statistically significant decrease in the median number of days for that first event. And then in terms of false negatives, you can see that's remained pretty steady at around 4 percent. These are folks that we pick up in the registry, and it -- it appears that they've been missed in some way by newborn screening.

Okay. This is -- this is actually where I became interested in newborn screening, because what we found was this ambiguous diagnosis. Actually, in the US, we've called it CRMS. In Europe, they call it CF-SPID. We've sort of harmonized, and we've landed on this CF-

SPID, this ambiguous diagnosis. You can't say they don't have CF, and you can't say they do. So, they're typically sweat -- intermediate sweat chloride values. And here's the point. If you -- when our care centers enter a new patient, there's a diagnosis case report form, and they can enter CF, CF-SPID -- those options are available. And then, we've recently updated our guidelines on diagnosis of CF with Phil Farrell's leadership and then we started looking at the data, and what we've seen, and I don't know if -- so, the guideline diagnosis is coming down. So, if you look across the registry diagnosis -- what was entered at the care center level -- look across that top line, the CF diagnosis; 126 of these ambiguous diagnoses by applying the guideline is being entered as CF, it's about 40 percent of CRMS patients. So, we don't know for sure. The clinicians may be smarter than us. But we suspect there's some degree of misclassification here, and we're working hard to try to educate our care center docs and staff about -- about applying the

guidelines. This, again, is where it caught my attention, because this, we need to be aware of in registry analyses.

So, to summarize, for us, the registry has been a highly impactful asset. We use it for multiple purposes and always looking for ways to leverage what is a very rich and granular data set.

Developing and operating a registry is labor and resource intensive, but the value continues to increase for us and, as mentioned, we consider it one of our crown jewels.

So, hopefully I've left some time for -- for questions and thank you for your attention.

DR. JOSEPH BOCCHINI: Dr. Marshall, thank you for showing us the value of the registry and all of the benefits it can provide. So, thank you. Let's open this for discussion. If the operator will open up the lines for organizational representatives, we'll give first questions to the committee. Dr. Tarini.

DR. BETH TARINI: Hi, Beth Tarini.

Dr. Marshall, it was my understanding -- to confirm my understanding and then I have a question -- it was my understanding that at one point in recent times, the CF Centers were de-identified as to their performance metrics. So, instead of saying Centers 1 through X, the actual names of the Centers were revealed, and there was a number of reasons for doing that, and there was -- to my understanding -- some resistance amongst the centers. Given in newborn screening there has been some resistance to releasing data in some instances because of the perception of the negative effects on performance trump the concerns that, you know, this will lead to improvement, what lessons did you learn in getting through that -- through that period that you can share with us?

DR. BRUCE MARSHALL: Yeah. I think you're -- it's a great question. Yeah, I think you're referring to the fact that we worked with colleagues at Dartmouth to develop sort of a risk-adjustment model, you might call it, and then for key metrics, this dates back, I think, to '06,

'07. We decided to display those on our website, and there was quite a bit of resistance. In the end, our care centers talked about, well, the risk adjustment doesn't account for this and for that, and people worried about patients would move from one center to another, and I should say clinicians, and clinicians worried about lawsuits. And so, we -- we prepared extensively for this event. I updated my resumé. I thought that I might have to leave the Foundation. But it -- and what -- one of the drivers really was for us to go in that direction was we thought it was the right thing to do. We thought it was ethical. The foundation was started by patients and families, still driven by patients and families. It's not -- we're not a medical society. And we -- the word was out that we had care center performance data. So, we would get a periodic E-mail about -- from a parent worried about their child, could you tell us the top centers. So, in the end, this was a process we went through internally, I would say, probably for 12 to 18 months, and then finally, we

just thought it was the right thing to do, the ethical thing to do. We talked through it with our care centers. We gave them long notice. We encouraged them to share their data -- their own data with their departmental and institutional leaders and to share it with their patients to sort of prepare for this event. And, to be honest with you, it proved to be a nonevent. There was really -- there's been no movement of patients from one center to another. I think there's a small slice of the patient population that -- that look at it, and they may choose a center for a second opinion, but we haven't seen mass migration. I think the one place where it has been used is by institutions. You know, they'll -- particularly kind of high-profile institutions, and they think that they should be near the top on the key metrics. If they look and they see that they're mediocre or average, there may be some additional investment of resources. So, I think it's been -- I think it's been a net positive for the community, and if anything, I think we're --

we're not transparent enough, you know, we need to go through the process again, and we have other data we know people are interested in. So, hopefully we can become more transparent. So, essentially, it became a nonevent. I'm sure there are ripples out there, but there was no major impact back on us.

DR. JOSEPH BOCCHINI: Dr. Baker, Dr. Powell, Dr. Barry.

DR. MEI BAKER: Mei Baker. Actually, I'm from Wisconsin, and I didn't even know that.

DR. BRUCE MARSHALL: You know Phil Farrell, I suspect.

DR. MEI BAKER: Very well. My question is regarding CRMS. I think it's very interesting you put that there. The thing of the justification of newborn screen identified CRMS, I think is because my understanding, I hear the ratio, I mean, the percentage is anywhere from 5 to 20 percent CRMS potentially changes to the classic or typical CF. So, I was wondering, in your registry, do you capture diagnosis change

over time, and also, it would be very nice to do such a research, so we gather more evidence.

DR. BRUCE MARSHALL: That's a good question, and we do -- we do track it. There is a means of changing diagnosis, and we haven't carefully looked at that in the registry, but there have been some publications on that, and it's probably going to be closer to the 5 percent rather than the 20 percent. But we do have that capacity to follow these folks over time. We -- we don't think we're getting all of them. You know, so there's some -- there's some bias. As mentioned, we don't get all the CF patients. There's some that don't -- that don't consent, but it's a relatively small number. CRMS, we think, the percentage that we don't get is higher. But we do have the ability to track, and we do see some changes to full-blown CF, but on the milder side. You know, they're not going to convert to a severe genotype. They're -- they're going to convert to that sort of pancreatic sufficient is what we think over time.

The folks that we've worked with, you've mentioned and you've very familiar with Phil Farrell. We've also worked very closely with Clement Ren, Suzanna McCauley, very interested in newborn screening. So, any wisdom related to newborn screening on our registry comes from those three folks.

DR. CYNTHIA POWELL: Cindy Powell. So, I have two questions. One is how do you control access to the registry? For example, if a committee such as ours wanted to get some information about the long-term benefits to children identified through newborn screening, how would one go about that? And then secondly, is -- regarding the long-term financial sustainability, I know the CF Foundation does a tremendous amount of fundraising, you've also been able to reap the benefits of some of the drug patents, I think, or in the past. But, you know, that only can go so far. So, long-term, how do you, you know, plan to continue to be able to support the CF Centers and this data entry?

DR. BRUCE MARSHALL: Yeah, good questions. I'll talk about the sustainability first. You're right. We, you know, we've been very fortunate. We have an abundance of resources. The registry was initially funded and sustained by donations, you know, it came through philanthropy, and still, it's -- it's still a source of support. One of the ways that we supplement that is through building post-approval research business on top of the registry. And what we found is actually the data we have is very valuable, and, you know, if the EMA or FDA mandates studies, the registry can be used as a basis for that study. Sometimes it doesn't even require any change. They'll just accept the data that we collect. So, that is trivial effort for us, and we develop a licencing agreement and we don't give it away, you know, we try to price it at market value. I mean, we, you know, we -- we scope it out. Our registry vendor is familiar with this space. They help us. It's like, okay, if pharma came to you, how would you price it out?

And then -- then we give them a little discount, so they don't go elsewhere. So, it's -- so that we generate quite a bit of revenue from that now, and it supports the operation of the registry. It doesn't support everything we do for the Care Center Network, but it can be a fairly generous source of revenue if you have new therapies coming through and they come with post-marketing requirements. And then, what was your other question?

DR. MEI BAKER: Access.

DR. BRUCE MARSHALL: Oh, access. Yes. We do accept external requests for data. If you E-mail me, I can put you in touch with the right person. There's a peer-review process, and we ask that you have some contact with one of the care center docs so, for example, Clement Ren, Suzanna McCauley, and anybody that has some association with one of our accredited care centers as sort of a co-investigator, you might say, just to help provide context for CF and so it's open to external requests, and we probably --

I don't know -- I think we probably provide about 20 to 30 data sets a year based on external requests.

DR. JOSEPH BOCCHINI: Because of time constraints, I'm going to give Dr. Berry the last question.

DR. SUSAN BERRY: I was particularly interested in the data entry element of what you described, and one of the things that's often been sort of a pipe dream for registry lovers is to be able to connect directly or in some way mine from EMR either through standard data sets or creating back spreadsheets or generating notes from data entry or any other element that facilitates documentation in the EMR and at the same time brings data into a data registry. Have -- as an opportunity with resources, have you guys explored this, and what progress have you made?

DR. BRUCE MARSHALL: Yeah, it's a great question, and we've actually explored it over the last several years and just in the last year, we launched a pilot that's ongoing now. We

have, I think, about five centers in that -- in that pilot, and we're working with our registry vendor on this. From a technical standpoint, it's certainly doable, but it is resource-intensive because it's all -- it's all one-off. Each center has their own compliance office and IT officers, et cetera, et cetera, and that's -- that's the burden, getting through that technical side of it is pretty straightforward. But, you know, we have about 280 programs, maybe -- maybe 180 distinct medical centers. So, you know, you start -- you start to add up the numbers on what it takes to get everybody online. So, where we've started the pilot is places that are significant size, that's going to save some effort. Where there's a link to the -- to the IT department and then we can get them engaged, and then some sense of the administrative burdens, how long it would take to get through their compliance office and sign off on the data-sharing agreements that we need to put in place. So, it -- we'll get there, but it's not -- it's a slog.

DR. SUSAN BERRY: Harder than it looks.

DR. BRUCE MARSHALL: Yeah, it's harder -- it's harder -- much harder than it looks. But the payoff could be enormous. I mean, we -- we -- we start to salivate about other data elements that we could -- like, for example, lab data. You know, that's all pretty well standardized. We could bring that data in. We get very little lab data now. Radiology. I mean, you could go on and on about what you could get to get to a very granular data set.

DR. JOSEPH BOCCHINI: Once again, thank you, Dr. Marshall.

DR. BRUCE MARSHALL: Thank you all.

DR. JOSEPH BOCCHINI: We really appreciate you coming to the committee. Thank you.

Next on the agenda is the presentation by Dr. Jennifer Puck, and it will be made electronically. Dr. Puck is on the line, and if we can pull up her slides. She is the

principle investigator of the Primary Immune Deficiency Treatment Consortium and will talk today about the Consortium's effort to gather data on SCID. After serving on the faculty of the University of Pennsylvania in Philadelphia and the National Human Genome Research Institute at the NIH, Dr. Puck joined the University of California, San Francisco, in 2006 as Professor of Pediatrics. She directs the UCSF Jeffrey Modell Diagnostic Center for Primary Immune Deficiencies and is well recognized as a leader in the field of Newborn Screening for Immune Deficiency Disorders. So, Dr. Puck, we have your slides ready, and you are ready to start.

PRIMARY IMMUNE DEFICIENCY TREATMENT CONSORTIUM

DR. JENNIFER PUCK: Yes, so good morning. Can you hear me?

DR. JOSEPH BOCCHINI: Yes, we can. Go right ahead.

DR. JENNIFER PUCK: Okay. Thank you. I'm very pleased to be invited and thank you for accommodating me to the schedule. So, if we could

advance to the next slide, I'm going to tell you a little bit about the Primary Immune Deficiency Treatment Consortium, which is one of the members of the Rare Diseases Clinical Research Network and these are consortia, which are joined together through the NIH Office of Rare Diseases, and we also include a Data Management and Coordinating Center that is mandated to store all the data collected by the consortia.

So, our major support is from the NIAID, but we also receive support from the Office of Rare Diseases within NCATS. And the goals of the PIDTC are to conduct natural history studies in SCID, Wiskott-Aldrich syndrome, and Chronic Granulomatous Disease, though I'll only be talking about SCID today.

Sites around the country and in Canada have applied for membership, and they are considered based on their experience and expertise, and we have had centers which have been underperforming, and they've been excused, and each year, we invite new sites to apply.

Now, the patient advocacy groups who have become a very important part of each one of the consortia in this Rare Disease Network, they've been critical partners with us from the start, including the Jeffrey Modell Foundation, the Immune Deficiency Foundation, and the SCID Angels for Life Foundation, of course, among others specializing in other diseases.

And if you go to the next slide, I hope this is the one with the map. It shows in the yellow dots where the 44 centers are in the US and Canada, and these centers have collectively enrolled by now 1,749 individuals with SCID -- sorry -- with all the immune deficiencies. And down below, you see listed our four current protocols, two of them concern SCID, and there is a prospective, longitudinal study that has enrolled nearly 300 and a retrospective and cross-sectional study with close to 750 enrollees at this time. So, the map also shows how newborn screening started in the darker green colors and then have spread so that as of last December, all

50 states were screening for SCID and the PIDTC takes pride in having helped this happen along with our many partners.

So, the next slide, I hope you're able to see it because on my MAC, it's totally blank. This shows the influence of introduction of newborn screening for SCID and the way that these get diagnosed. And on top, I just put a reminder of what the SCID newborn screening test consists of, which is looking for T-cell receptor excision circles, which are biproducts of normal T-cell development. And when the number of these circles is too low or undetectable, infants are called back according to each state's individual newborn screening protocol, and they are evaluated for immune deficiency, and a number of these do turn out to have SCID. So, the lower graph on this page shows the percentage of cases enrolled in the PIDTC from 2010 to 2016, and the green line shows you the number who were diagnosed based on newborn screening, while the red line shows the decrease in cases diagnosed because of infections,

which used to be the predominant way SCID was diagnosed.

Now, next slide. One of the very important things about the PIDTC is it functions with a central IRB, and this is now mandated by NIH for multicenter clinical studies that they support, although our Canadian sites don't have to participate. And so, in this case, the UCSF IRB is the IRB of record, and this has been a huge task to get on board all the IRBs from all the different sites. But it certainly is facilitating the enrollment of subjects and the promotion of changes to the protocol where necessary. We can make amendments very easily. And so, we're really actually taking advantage of these reliance agreements to streamline the PIDTC enrollment.

So, we have elements of the registry that are consented -- every patient in the prospective part of the study in the consortia is consented. However, if it's purely retrospective, we have waivers in place to record the identified patient data and in our cross-sectional group, of

course, that's consented also for the procurement of samples.

So, the first thing that the PIDTC had to do was actually come up with definitions for SCID for eligibility purposes, and I think people in this group are probably familiar with our eligibility criteria, because they were the same as what was used in the 2014 publication and they're outlined here that there's typical SCID, leaky or atypical SCID, and Omenn syndrome, and of course there's the unfortunate variant term that was initially used, and we don't find that very useful, actually, that we don't have a good definition for that, but we determined eligibility for PIDTC by treating into one of these criteria. We actually have a Review Committee that reviewed each prospective or each potential enrollee for eligibility.

Next slide. So, this slide shows where the data comes from that we collect. The CIBMTR, which is the Center for Internal Bone Marrow Transplant Research, this is the legally

mandated organization that collects all USA transplant data and a fair amount of international transplant data as well. And this data is -- there are actually two levels of reports for CIBMTR transplants. There's a simple form and then a much more extensive research form, and so we require that the research form be filled out in CIBMTR for all the PIDTC patients who are entered, and this includes very detailed data about the donor and recipient HLA type, the conditioning, and all kinds of data related to the transplant. And the PIDTC itself has developed a whole series of case report forms with their titles listed here, and they are also filled out by each center enrolling a patient. And the data from both these sources are combined into the database, which is in the DMCC.

Next slide. So, in addition, we also have samples that are collected for study in specialized centers, and this is just an example of a few of the studies. All of the enrollees have dried blood spots sent for TRECS

determination and these are done sequentially. You can side effects at the bottom there, done at the baseline 100 days, 6 months, 1 and 2 years, and we also collect RNA in a PaxGene tube for spectratyping to measure T-cell diversity. And this has been done since the start of the study in 2009.

We also have different pilot programs. Often, we fund young investigators to undertake these, and these pilot studies have become core elements that have been incorporated with amendments to the overall protocol. And so, for example, looking at B-cell development after transplant, looking at the phenonemon of T-cell exhaustion in some patients whose transplants ran out of steam after a period of time, and other things. And of course, all the sample tracking is done through the DMCC, and all these results are deposited there.

Next slide. I hope you can see this, because I can't see it on my screen. But I put in a couple of screenshots of the kinds of online

data collection forms so that you can get something of a flavor for them, not that you're supposed to read them. We use drop-down menus as much as possible, and we have used standardized terminology to make our data entry operable with other data.

Next slide. And this shows some of the important overview core publications from the SCID protocol that we have put together, and I -- I think that these have been highly cited. They're also widely -- they are the largest studies separating different genotypes of SCID, because prior single-center studies had to log them together because there were never enough cases in a single site to do good statistical analysis, and, of course, we're continuing to work on these.

And then I just thought I'd end up with a couple of examples of what we hope to do in PIDTC in the future. So, the next slide, and this is of course hoping that we're going to be funded for another cycle, which our current cycle ends at the

end of August of this year. So, this is all representing hope that at this point in time. But we will incorporate genetic and pathogenic evaluations of newly diagnosed SCID patients. Many of these today are getting gene panels right from the start that established their diagnosis, but in 10 percent of the cases, they did not have a diagnosis even after clinical laboratory whole exome sequencing. And so, we're going to make a concerted effort to study these cases in detail with family trio, whole genome sequencing, gene expression studies. We know that the patients may not have T-cells, but their parents do, and if they are heterozygous for deleterious mutations, their T-cell expression will reflect this. So, that's going to be looked into. And we will develop candidate variants and then they will be studied in particular laboratories with expertise depending on what they show. For example, in some cases, we know that there are actually thymus defects rather than defects in the bone marrow stem cells leading to inability to make mature T-

cells.

The next slide shows a quality of life study that we're undertaking and actually this is already starting. We're using the PROMIS Pediatric Self-Assessment Tool because these are widely validated and also available in Spanish as well as English, and the DMCC has provided these to all of the members in the NBSTRN. So, depending on the individual's age and also following over time the different ages, we will administer these tools, and I think this is really important, because survival is the only measure that has been published widely before. And, of course, that barely scratches the surface, and we're very concerned about quality of life.

Next slide. And finally, we've determined that despite newborn screening, we have not gotten rid of infection in SCID, and sort of a shocking finding was that 40 percent of SCID infants, even though they were diagnosed by newborn screening, had developed an infection before their transplant, and some of these are not

so terribly serious, but cytomegalovirus is one organism that is very serious and has been fatal even in newborn screened cases. And so, we know that this can be transmitted through breastfeeding, also in maternal secretions at delivery. And so, we're going to undertake a prospective natural history study to look at which mothers are CMV positive, and we're going to try to do PCR in breastmilk samples to look at excretions. We're going to follow these infants. And this is a study that is going to lead to a clinical trial for prophylaxis with some of the newer anti-CMV agents that are more effective and perhaps less toxic than agents currently available.

Next slide. Just to wind up, I want to thank very much the RDCRN and also NIAID for supporting us.

And the final slide, shows Mort Cowan, who is our Inaugural PI, and he's dedicated to raising a new generation of leaders in Primary Immune Deficiency, so I think this is actually one

of the -- the individuals we're grooming to be an immunologist in the next generation, and he's a recipient of gene therapy for SCID. So, I'm happy to take any questions. Thanks.

DR. JOSEPH BOCCHINI: Thank you, Dr. Puck. We appreciate your participation and your introduction of the next generation of immune deficiency experts. Thank you. So, let's open this up again. Operator, open the lines for the organizational representatives, and first question is to the committee. Dr. Berry.

DR. SUSAN BERRY: Hi. This is Sue Berry. Jennifer, thank you for that summary, which is really exciting and the kind of progress that's been made. The question I have for you is that in the most recent round of competition for the RCDNs, one of the adjournments to create plans for sustainability for maintaining these Rare Disease Networks, and I was wondering what concepts you guys might have employed, and how you see that future going forward, because ten years is not very long in natural history.

DR. JENNIFER PUCK: Well, you're right. And so, we hope that we'll get another five years of support from NIH, and I must say, this support, while invaluable, has always been insufficient. But we couldn't at this point survive without it. We look to the Cystic Fibrosis Foundation with great envy and admiration, and we are working with our Patient Advisory Group partners and trying to establish a future, because what we see is that we need to evolve into a Clinical Trial Network for Primary Immune Deficiency, not just a data collection venue. And so, when we do that, we certainly hope to enlist corporate participation and gene therapy has really started to move from clinical trial stage to standard of care, and I believe that during the next three to four years, there will be standard of care treatment for X-linked SCID, adenosine deaminase deficient SCID, and also artemis deficient SCID with gene therapy. So, involvement of corporate partners to have participants in those trials is -- is important.

We're also looking forward to development of substitutions for chemotherapy. As everybody knows, chemotherapy is toxic but required to get stem cells to engraft, and stem cells have to be there in order to produce B-cell function and full reconstitution and a long-term cure, and there are monoclonal antibodies coming online to -- to be assessed, and again clinical trials must be conducted. We are positioning ourselves to be the organization in which these take place. So, I hope that these will help in that aspect.

If anybody has any other ideas, I'd love to hear them.

DR. JOSEPH BOCCHINI: Thank you. Are there any additional questions, comments from the committee or organizational representatives? Individuals on the telephone? Hearing none, Dr. Puck, thank you very much for your presentation. We know you have to get to clinic this morning. So, thank you for taking this time before clinic to talk with us. We appreciate it. Thank you.

DR. JENNIFER PUCK: You're very welcome.

DR. JOSEPH BOCCHINI: All right. So, we are right on schedule. Our goal was to have an early lunch today, and then come back with the rest of the meeting. So, we are going to take a 45-minute break for lunch -- just under 45 minutes. We want to see if we can get back at 12:15 to start promptly at 12:15 for the next portions of the agenda. So, thank you very much.

LUNCH BREAK

[Off the record at 11:30 a.m.]

[On the record at 12:15 p.m.]

DR. JOSEPH BOCCHINI: We'll now begin the afternoon session. All right. Let's welcome everyone back to the afternoon session of today's meeting. I'm going to start again with roll call. We'll start with committee members on webcast. Kamila Mistry.

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Mei Baker.

DR. MEI BAKER: Here.

DR. KAMILA MISTRY: Dr. Bocchini, could you hear me?

DR. JOSEPH BOCCHINI: Yes, we heard you and we got you for this morning, too, so.

DR. KAMILA MISTRY: Okay. Thank you.

DR. JOSEPH BOCCHINI: All right. Sue is not back yet. I'm here. Jeff is unable to be here. Kyle Brothers.

DR. KYLE BROTHERS: Here.

DR. JOSEPH BOCCHINI: Jane DeLuca.

DR. JANE DELUCA: Here.

DR. JOSEPH BOCCHINI: Carla Cuthbert.

DR. CARLA CUTHBERT: I'm here.

DR. JOSEPH BOCCHINI: Joan Scott.

MS. JOAN SCOTT: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi.

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Cindy Powell

DR. CYNTHIA POWELL: Here.

DR. JOSEPH BOCCHINI: Scott Shone.

DR. SCOTT SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini.

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: Catharine Riley

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: All right. Now, for organizational representatives. Robert Ostrander.

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: Debra Freedenberg is not yet here. Michael Watson.

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: Britton Rink by webcast. Jed Miller.

DR. JED MILLER: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley.

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus by webcast.

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Natasha Bonhomme.

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: That was quiet,

okay. Siobhan Dolan by webcast.

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: Cate Walsh Vockley.

MS. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: Shawn McCandless has not made it back yet. Okay. So, we've got Dr. Berry. Okay. All right.

We're going to begin this session with the remaining public comments. So, we have four individuals who will present public comments, and we would ask each of you to come forward to the podium as you make your comments. So, first today is Dr. Emmanuèle Délot from Children's National Medical Center.

PUBLIC COMMENTS:

DR. EMMANUÈLE DÉLOT: So, thank you so much for the opportunity to present in front of this board. I am Dr. Emmanuèle Délot from Children's National Medical Center in Washington, and I'm here representing the DSD Translational Research Network, DSDTRN. The DSDTRN is an NIH-

funded national network of clinics and research centers dedicated to improving management and service to patients with disorders of sex development. I serve as the National Coordinator for the network as well as the Director of Biobank and the Chair of the Publication and Research Committee. And I'm here to present the project headed by Professor Phyllis Speiser of the Hofstra School of Medicine in New York on behalf of the principle investigators of the network, Eric Delayne at Children's National in DC, and David Sandberg at University of Michigan, and the Endocrine Workgroup of the Network, in particular our endocrinologist at the Phoenix Children's Hospital, LeBoneur, Memphis, Lurie Children's in Chicago, Washington University in St. Louis, and Cincinnati Children's.

I'm not going to teach anyone about congenital adrenal hyperplasia, but CAH is caused by 21 hydroxylase deficiency is the most common disorder of steroid synthesis and is recommended as part of newborn screening in all US programs

because early diagnosis and treatment prevents morbidity and mortality in infants. The filter paper blot specimen typically collected in full-term infants on day 2 are subjected to a thorough amino assay called Delphia to test for levels of 17 hydroxyprogesterone, 17 OHP. However, prematurity, low birth weights or critical illness are known to cause falsely elevated results and reduce the test's positive predictive value, and these findings were included in the new clinical practice guidelines for management of CAH that were published last year by the Endocrine Society, an effort also led by Dr. Phyllis Speiser.

We initiated a survey of state protocols as a preliminary step to quality improvements and analysis of the ten data sets that were returned revealed that each state has a different procedure for identifying and reporting positive newborn screens. For example, nine out of ten states used birth weight-based cut-off points and only one state used gestational age. Cut-off points for normal results varied widely.

For example, for birth weight between 2,250 and 2,500 grams, the cut-off 17 OHP value varied from 25 to 75 grams per mL, which is a three times difference. Our survey also showed that the amino assay was associated with low positive predictive value, and this value varied from 1.2 percent to 9.6 percent, revealing differences in sensitivity and specificity of screening among states.

So, in conclusion, there is a need for standardization of newborn screening protocols for CAH to improve the positive predictive value. There are published reports that a combination of birth weight and gestational age may provide up to a ten-fold improvement in positive predictive value and that using tandem mass spec enhances the value of confirmatory testing for paper filter samples.

These preliminary results received a lot of attention when they were presented last month at the Endocrine Society Meeting in New Orleans. Our plan is now to complete the survey of states, and we respectfully hope that the board

would encourage this effort and consider our results. Thank you.

DR. JOSEPH BOCCHINI: Thank you very much for this presentation and bringing this survey to our attention. We look forward to its publication. We'll take the results and look at them seriously. Thank you.

Next on the agenda is Ms. Brittany Hernandez with the Muscular Dystrophy Association.

MS. BRITTANY HERNANDEZ: Thank you, Dr. Bocchini. My name is Brittany Hernandez. I'm the Director of Advocacy for the MDA, and I want to thank all of you for the opportunity to speak today and also welcome Dr. Powell as the incoming Chair. We're really excited to be working with you going forward, but obviously sad to be closing out this chapter with Dr. Bocchini.

I also want to thank the committee for its commitment to screening -- newborn screening for neuromuscular conditions. The addition of Pompe and SMA to the RUSP is something that's been really important for our committee,

and we've seen a lot of movement forward after those conditions have been added.

MDA is an umbrella organization covering over 40 different neuromuscular conditions. We have over 150 care clinics across the country at some of the leading medical institutions that care for individual with all of the conditions under our umbrella. These are multidisciplinary care clinics where individuals can go to get all the services that they need -- both medical and social support services.

We also support the new data hub, the Neuromuscular Observational Research Data Hub called MOVR, which is our new clinician data registry. Right now, we launched it tracking four different neuromuscular conditions. They are ALS, Duchenne, SMA, and Pompe disease. We know that this new registry is going to help aid in development of clinical trials for individuals with neuromuscular conditions including Duchenne, which is obviously one part of why we have an interest in adding DMD to the RUSP. We're working

collaboratively with partners across the spectrum on a DMD RUSP nomination going forward, and we're proud to be partnering with a number of other individuals and groups on this. We understand that there might be some concerns about utilizing CK for -- for the detection of Duchenne since it could lead to -- since it would lead to detection of other conditions. But we would offer that the MDA Care Clinic Network does exist to provide care to all individuals identified with a neuromuscular condition, including those that could be identified via a CK test for Duchenne.

MOVR will also build and track progress of NBS-identified patients with Duchenne and other related conditions through the CK test, and we also are working on generating a number of different medical education initiatives for physicians that work in our clinics to ensure that they know how to care for patients who are identified via the newborn screening process. We have a number of staff on board who are working closely on that, and I'd be happy to make any

connections should you have questions about the efforts that we're undertaking to make sure that physicians are as informed as possible to help them take on any babies and families who are identified via the process.

I want to thank the committee for its commitment to newborn screening for neuromuscular conditions and I appreciate the opportunity to share my comments today. Thank you.

DR. JOSEPH BOCCHINI: Thank you, Ms. Hernandez. We appreciate your efforts and look forward to the nomination packet when it's completed.

Next is Ms. Annie Kennedy with Parent Project Muscular Dystrophy. Ms. Kennedy.

MS. ANNIE KENNEDY: Good afternoon. I am Annie Kennedy with Parent Project Muscular Dystrophy or PPMD, and I'm here today representing the National Duchenne Community. Last month, I had the opportunity to present before this committee to share that PPMD, along with a pretty competitive consortia of funding partners, has

initiated a Duchenne Newborn Screening Pilot in New York State, and Mike Watson alluded to that earlier today. Today, I'd like to spend a few minutes focusing on the publications, tools, and resources that we've worked with collaboration with our partners to build to support families and providers who will be working within that pilot.

Over the last decade, PPMD has collaborated with the Centers for Disease Control and Prevention and the American Academy of Pediatrics on several efforts designed to develop diagnostic and clinical care tools and resources for providers and patients. In 2009, PPMD received funding through a cooperative agreement of the CDC to convene the National Task Force for the Early Identification of Childhood Neuromuscular Disorders to address the delay that families frequently experience between symptom onset and diagnosis of neuromuscular disorders. The taskforce aimed to increase clinicians' awareness of peripheral neuromuscular disease as a cause of developmental delay in young children and

to help providers in primary care, rehabilitation medicine, and physical therapy identify the early symptoms of neuromuscular disorders. The taskforce included representatives from the American Academy of Pediatrics, the American Academy of Neurology, the Child Neurology Society, Cure SMA, MDA, and NSGC, the American Physical Therapy Association, and many others. The yield from the effort was the creation of training tools, diagnostic and clinical algorithms, and clinical support tools, all housed on the website, childmuscleweakness.org. The effort also included a year-long dissemination program.

Following that in 2016, PPMD, the American Academy of Pediatrics, and the CDC partnered to develop a motor delay assessment tool for parents through a program called Learn the Signs, Act Early. That, again, is housed on AAP's website.

In October of 2018, the AAP dedicated a supplement of their journal to a series of 13 publications featuring expanded care guidelines in

Duchenne entitled Specialty to Care for the Patient with Duchenne Muscular Dystrophy. Included was a primary care and emergency department management in the patient with Duchenne muscular dystrophy article. There will be a webinar on that later this week, actually, for primary care providers.

Also, in October of 2018, a refined ICD-10 code for Duchenne and Becker MD was implemented within the CMS addenda. This effort was led by PPMD with support from the CDC, CMS, and AAP. And currently, a new action sheet is being developed by NBSTRN and their clinical integration group as a part of the Duchenne Newborn Screening Pilot in New York State.

Despite all of these efforts, our surveillance data continues to reflect an unnecessary and heartbreaking diagnostic odyssey that delays access to care and impacts outcomes for our families. Last March, PPMD convened an externally led patient-focused drug development meeting with the FDA in Washington, DC for a

powerful day of testimonials from families about their current experiences with Duchenne. Throughout that day, parent after parents described their journeys from parental concerns to confirmed diagnoses. The descriptions included recollections of having worries brushed aside by clinical providers, months and even years of inconclusive tests and therapies, and diagnoses delivered with little or no information about Duchenne and no direction as to where to turn for expert care and support. And while this was not everyone's experience, it is the rule rather than the exception.

I'd like to take a moment to read an excerpt from a few of the parents' testimonies now to capture the common diagnostic experience. Particularly striking to me is that these parents came into our community after the previously mentioned clinical resources had been created and disseminated.

This from Lisa in Nebraska. "I'm a stay-at-home mom of three. Prior to having

children, I was a full-time physical therapy assistant. In January 2014, just after Lane's second birthday, we requested therapies for Lane from our local primary provider for speech delays as well as growth and fine motor delays. After doing some research, I had also requested a CK blood draw, and I'll never forget that phone call when the results were reported back. The nurse who called me actually asked me if he should be hospitalized. It was in that moment, during that diagnostic call, that the nurse -- with the nurse that I became the educator for others about Duchenne."

And this one from Clair in St. Louis. "On Friday evening, December 30, 2011, we were getting ready for a family Christmas party, when I received a call from our pediatrician's office. Earlier that week, the doctor had ordered blood tests after Henry's teacher had requested a PT referral. Although I'd raised concerns in the past about his inability to jump or climb, I was always assured that kids just develop at different

stages. Over the phone, the doctor shared that the lab results indicated Duchenne muscular dystrophy. In my mind, it scrambled to recall what I knew of Duchenne. He said, "It was bad," and told me that I would find more information online. Our vacationing pediatrician said he would refer us to a neurologist after the long holiday weekend. That evening, my happy babies went to the party with my sister, while our world crumbled into pieces. My husband and I wept at the prognosis that we found on Wikipedia. This dark night marks the before and after of our family's life."

Our community's goal through our newborn screening program is that no family ever be subjected to an unnecessary diagnostic odyssey again and that every family receive timely supportive resources at the time of diagnosis. The Duchenne Newborn Screening Pilot Program is designed to set up, validate, and conduct a consented pilot screen for infants born at select hospitals in New York State, which will utilize

tools, resources, and expertise at PPMD and the Newborn Screening Translational Research Network and the New York State Department of Health. This pilot is being funded through a unique model in which PPMD has converged a pre-competitive consortia of biopharmaceutical industry partners with a commitment to early diagnosis and intervention in Duchenne. In addition, the pilot is being guided by a Steering Committee comprised of representatives from federal agencies, provider groups, and representatives from key Duchenne stakeholder communities. This is an important inflection point for us in our community and one that we recognize we would not have reached without the guidance and support of all of you. We are grateful and most of all our Duchenne community is hopeful. Thank you.

DR. JOSEPH BOCCHINI: Thank you, Ms. Kennedy, for your presentation and we look forward to the results that come from the New York pilot study. Thank you.

Next is Rebecca Abbott with the March

of Dimes.

MS. REBECCA ABBOTT: Good afternoon, Dr. Bocchini, and members of the Advisory Committee. Thank you for the opportunity to speak today. My name is Rebecca Abbott, and I am the Deputy Director of Federal Affairs at the March of Dimes. In that capacity, I have the privilege of spearheading a group of more than a dozen organizations, many of them represented in the room today, dedicated to advancing newborn screening through national policy.

Over the past few years, our coalition has focused on insuring that Congress provides increased funding for newborn screening programs at CDC, HRSA, and NIH. I am pleased to report that we have been successful in those efforts. In fiscal year '19, Congress provided $10 million more to CDC and HRSA than they had in fiscal year '17. We will continue our work through the annual appropriations process and are hopeful our success continues.

In addition, our perennial activities

supporting appropriations, last year our organizations began laying the ground work for Newborn Screening Lives Act Reauthorization, which expires on September 30th of this year. Our coalition developed a set of shared principles to guide reauthorization and shared our recommendations with Congressional champions. After months of refining language, I am pleased to report that the Newborn Screening Saves Lives Act Reauthorization of 2019 will hopefully be introduced in the House next week.

Our long-time champions, California Congresswoman Lucille Roybal-Allard and Congressman Mike Simpson will again sponsor the bill. As Dean mentioned yesterday, the bill will raise authorizations for programs at CDC and HRSA and makes very targeted refinements to language governing activities of CDC, HRSA, and NIH. It will also commission a report by the National Academy of Medicine, looking at the future of newborn screening and of particular interest to this committee, it will extend your charter for

another five years.

On the Senate -- our coalition is pleased with the language and looks forward to advocating for its swift passage. On the Senate side of the Capitol, our coalition is working closely with our new champions this year, Senator Maggie Hassan of New Hampshire and Senator Cory Gardner of Colorado to finalize language, and we are hopeful that legislation will be introduced before the Independence Day holiday.

Congress has much on its agenda this year, but we are confident that we can build the support to ensure reauthorization of the Newborn Screening Saves Lives Act, and that is on its to-do list. I will be here today, and I am always available to answer questions about the bill or our efforts. Further, our informal coalition is open to patient, provider, and public health organizations that are dedicated to newborn screening, and I am happy to talk to you about how to get involved.

Before closing, I wanted to take this

opportunity to extend a thank you on behalf of the March of Dimes to Dr. Bocchini for his leadership of the Advisory Committee and for his commitment to the health and well-being of children. Dr. Bocchini has served this committee with distinction, and our nation's newborn screening program and by extension our nation's children are better because of his service. Dr. Bocchini is also a long-time committed volunteer of March of Dimes. His volunteer leadership has been essential to helping our organization improve the health of moms and babies throughout Louisiana. So, Dr. Bocchini, March of Dimes thanks you for your service to this committee, to our organization, and to the mothers, infants, and families in Louisiana and across the nation. Thank you.

DR. JOSEPH BOCCHINI: Thank you for those kind words and thank you for updating us on the status of the reauthorization. We appreciate that. Thank you.

Next on the agenda is our

presentation from the Followup and Treatment Workgroup. It's an update on their activities and the work that they completed yesterday. Dr. Chris Kus will present by phone on the activities of the workgroup. Chris, let's see and make sure your line is open. Can you hear?

DR. CHRISTOPHER KUS: I can hear. Can you hear me?

DR. JOSEPH BOCCHINI: We can hear you.

DR. CHRISTOPHER KUS: Great.

DR. JOSEPH BOCCHINI: And your slide is up, so go right ahead.

FOLLOWUP AND TREATMENT WORKGROUP UPDATE

DR. CHRISTOPHER KUS: Okay. Again, I'm Chris Kus, and I'm pinch-hitting for Jeff Brosco, who couldn't be here today. Next slide.

DR. JOSEPH BOCCHINI: We're moving them forward for you, so you're fine.

DR. CHRISTOPHER KUS: Okay. Okay, got it. Start out with this just gives you a listing of the members of our Treatment Workgroup,

and we welcomed several people yesterday, and you'll see their names that are in red. Again, Jeff Brosco is the Chair, and I'm the co-Chair.

Next slide. During our workgroup meeting, we had two presentations, and I'll give you a flavor for each of them. The first one was on the Newborn Screening Translational Research Network that Amy Brower presented and specifically talked about the use of the Longitudinal Pediatric Data Resource, which is a tool that enables clinicians, researchers, parents, and patients to enter health information in a secure centralized system, and one of the works they've been doing along with NewSTEPs is working on if we looked at collecting long-term followup information from states, what might we collect. So, the goal of what they were doing was to create a minimum set of questions and answers from the Longitudinal Pediatric Data Resource for use by state newborn screening programs, and Amy discussed the idea that they had over 2,500 questions that they wanted to whittle down to 4 questions. Tough job.

Okay. Next slide.

DR. CATHARINE RILEY: Dr. Kus, this is Catharine Riley. There's about a ten-second delay if you're watching the webcast, so.

DR. CHRISTOPHER KUS: Okay, I got it.

DR. CATHARINE RILEY: Yep.

DR. CHRISTOPHER KUS: So, I'll start as you're going. Okay. Yeah. The next presentation was by Marci Sontag from NewSTEPs, and particularly, they were working with the Newborn Screening Translational Research Network to come up with the idea of having a minimum question set for public health, and the ones that Marci proposed were diagnosis, date of appropriate first intervention, are they alive, and within the last 12 months, did the child receive care and treatment specific to the diagnosis, and type of care provider.

Amy also -- Marci also presented on some of the work that they've done in terms of state profiles, getting a handle on what's going on with regard to long-term followup. Some of the

questions they're looking at are first, which we always talk about, regarding long-term followup, who is responsible, what is the data, how long do we follow up, and why do we follow up. And when they looked at the -- the information from -- from states and other programs, they -- they had information on 53 newborn screening programs from the 50 states, from Puerto Rico, and Guam, and 28 of those -- of those reported doing long-term followup while 25 reported no long-term followup. They looked at what types of long-term followup are out there, and they classified it into three groups -- basic, intermediate, and comprehensive. Basic being up to three years where they're collecting information about basic health status, access to care, and feedback from specialists. Intermediate would be up to five years with some clinical outcomes, some groups incorporate parent surveys, and information from management by specialist. And then comprehensive, they would be talking about followup going on from 5 to 15 years or more with more detailed outcomes and ensure

access to care including payment for formula.

Marci presented the question, who is responsible for long-term followup, and in her slide, she had listed states including management of access to formula and foods, newborn screening programs with information from specific tertiary care programs, children with special healthcare needs programs, case management programs through the state, and others.

She also presented what I've listed -- those four questions. She also presented an expanded question list that would be for treatment. The answer would be yes or no, but there would also be a reason reported for no treatment in the last 12 months such as no access, no health care provider availability, no insurance, other things. For the alive question, there would be information about cause of death, injury, medical, unknown. For developmentally appropriate, yes or no, unknown, whether they're getting speech, physical therapy, or other services, and then some question about how many ER

visits in the last 12 months.

Next slide. So, the question that we're posing for the committee's input is the issue of minimum data set, and would the committee approve the Followup and Treatment Workgroup thinking about a proposal that would encourage states to utilize a minimum data set for program evaluation using the work that I mentioned before.

Next slide. We also had a discussion on consent and confidentiality, and I just listed some of the issues that people mentioned. We did have a discussion of the risk of potential harm of identifying individuals. There was a comment that in smaller states, it is a significant concern. Communities vary in their willingness to consent to share their information. The specific statement made that labs can be a barrier to consent and the importance of letting families know that part of any consent is the ability to reconsider consent throughout the study period.

Last slide. We had such a rich discussion, Dr. Bocchini, we weren't able to go

over the input on key aspects of Dr. Kemper's presentation, but we intend to do that at our next workgroup call, and we also are going to follow up the discussion on the minimum data set based on this meeting. That's it.

DR. JOSEPH BOCCHINI: Chris, thank you very much. That was a nice presentation that made very clear what -- what you've been working on. Let's go back a couple of slides to the question that Chris has raised for the committee and open the discussion from the committee -- thoughts, questions for Dr. Kus. Scott.

DR. SCOTT SHONE: Scott Shone. So, I'll just say quickly about the question, I mean, it seems to make a great deal of sense. To use a minimum data set, it's impressive to think about truncating down 2,500 questions to 4. So -- but -- so, I mean, I -- in terms of program evaluation, a minimum data set seems to make sense, and I think there's precedent. Chris talked about Marci's data presentation. Obviously, I wasn't there, but, I mean, I'm not familiar with the

data. So, it -- it seems to me to make a great deal of sense.

I do have a question for Chris, though. You just threw out there that labs can be a barrier to consent, and I'd like you to elaborate a little bit on what that means.

DR. CHRISTOPHER KUS: Thanks for the question, and I have the information right in front of me. Here -- here's what the statement that was made that labs can also be a barrier to consent. Now, I didn't necessarily make the statement, but somebody in our group did. Some labs see their data as so valuable that they don't want to allow others to have research opportunities. Other state labs are unnecessarily afraid of violating HIPAA. And one of the responses from our group was that we could offer to help educate state labs and the public that they can consent to share their data and be clear about, you know, HIPAA concerns.

DR. SCOTT SHONE: Okay. I might suggest that it's not the labs themselves that are

the barrier to consent but perhaps the -- the -- the regulatory environment in which the individual lab is currently existing that has generated a concern of -- and I agree -- sort of a misappropriate concern around HIPAA or a violation of consent. And so, I would -- I appreciate you clarifying in terms of it's an opportunity to educate perhaps on the opportunities and the benefits of data sharing and perhaps frame it as a positive and what we could potentially do as opposed to the way it's phrased on your slide. Thank you.

And I don't think there's any laboratorians in your group, which is why I feel obligated to stand up for the laboratorians in the room.

DR. CHRISTOPHER KUS: I -- I appreciate that. Good comments. We had a rich discussion, and I think the -- I think the positive aspect of educating people, particularly, you know, as you mentioned, the idea of HIPAA. A lot of people's understanding are HIPAA are

incorrect.

DR. JOSEPH BOCCHINI: Other questions or comments? Okay. So, Natasha.

MS. NATASHA BONHOMME: Natasha Bonhomme, Genetic Alliance. Just to add to that, this was a topic in terms of what states can and can't do or how they relate to HIPAA. It came up quite a bit at our Newborn Screening Summit last year or two years ago -- our Education and Engagement Summit. So, we have some notes on the discussion that was there, and we had two HIPAA experts. So, we're happy to share that if that would be helpful with this workgroup or any others interested in that.

DR. CHRISTOPHER KUS: Yeah, that would be great. Thanks.

DR. JOSEPH BOCCHINI: Other questions or comments? So, I'm going to leave this question for Dr. Powell to chew on. And then, so that final decision can come from she and the committee going forward. So, Chris, thank you very much for your presentation, and I look forward to the

continued work of this workgroup. Thank you.

Next, we have the report from the Education and Training Workgroup. Dr. Tarini will provide us with the update.

EDUCATION AND TRAINING WORKGROUP

DR. BETH TARINI: Thank you, Dr. Bocchini. So, we also had new members. I also chose red to highlight them. And you see here we have Jane DeLuca, Sylvia Mann, Maa-Ohui Quarmyne, and Samantha Vergano, who we welcome to the committee. And I think I didn't get to the specific expertise here, but we have a very rich committee with the voices representative of a number of stakeholders across the Newborn Screening System.

So, we started our discussion with current member activities, which were very informative. Natasha Bonhomme talked about the Newborn Screening Family Education project that she is working on and is nearing completion of a needs assessment of 500 parents regarding their health information preferences and their usage,

and she anticipates completion of that project by the end of summer, I believe. And we've asked her to return to us with that as well.

Aaron Goldenberg and Keri LeBlanc have chaired an initiative that developed an education best practices framework to help facilitate development of educational resources. You can find this framework on babysfirsttest.org. I have the link here, and I have two slide sets to give you a sense of what that is, particularly helping with guiding questions -- what, why, who, when, and how when preparing educational resources as well as an in-depth pathway taking you through what an example is, giving a newborn -- using newborn screening implementation pathway and examples. These are both on that website. And, I believe, Iowa and California were the two states -- is that right -- is that right?

MS. NATASHA BONHOMME: Texas and New York.

DR. BETH TARINI: And New York. I thought Iowa used this. I have Iowa on the brain

-- it's still in Iowa. So, at any rate, those who would be interested in using it and providing feedback, please do so.

Yvonne Kellar-Guenther from NewSTEPs discussed the video tutorial that she's working on with the group regarding midwife-client discussions about newborn screening and the expected completion for that is summer/fall.

And Cate Walsh Vockley spoke with us about training programs for midwives in Pennsylvania, particularly around CCHD screening and donated pulse oximeters for all so there was full coverage for them.

We then had a presentation Mary Kleyn, who is the Michigan Newborn Screening Program Manager regarding a general information sheet for parents following positive screen. She presented on this developing project. This is an in-development information sheet that PCPs would use and provide to parents following a strong positive screen. It would also accompany a disease-specific fact sheet that is already

provided. And this information sheet contains a resources area to direct parents to websites that would provide helpful information regarding the disorders, an area where families could write down questions to bring to their confirmatory appointment with the specialist, and information about public insurance programs for children that could be used to cover confirmatory testing costs if they arose.

So, we had a rich discussion around this project and there were a number of potential collaborations in the room about how we can move this forward or help in any way. We also discussed the relevance of this project to the Ad-hoc Workgroup activities and if there were potential synergies that could be leveraged. And so, I have connected Dr. Kleyn -- I mean I've connected Dr. Baker with Mary Kleyn.

We discussed and debriefed the condition nomination evidence review process discussion through the lens of education and training and our charge as such. The main focus

of that discussion was on terminology, and the group felt that as far as educational efforts are concerned, that a shared and consistent terminology is the bedrock of any educational efforts around this process, and they echoed concerns about the use of target -- the term target to describe identification of unintended conditions, what we discussed yesterday during the committee.

And finally, we also discussed the Ad-hoc Workgroup results and education briefly, and we discussed thoughts about borrowing from existing efforts -- I mentioned Mary Klyne's effort in Michigan, the CLSI Workgroup efforts, especially around terminology -- and the potential future value from this effort, not necessarily as an immediate result but long-term, particularly development of templates that could be used regarding these issues across newborn screening stakeholders.

And finally, our specific projects have been completed -- our Education and

Communication Guides -- and we are working to disseminate it to the channels that the numerous members have and their areas of expertise and contacts. We are off-cycle, if you will, in our projects, and so next steps, we will work with the committee and HRSA regarding new initiatives for our committee that would be most helpful for the community and the committee. Any questions?

DR. JOSEPH BOCCHINI: Thank you, Beth. Let's open this for questions, comments, including those who are on the telephone. All right. Hearing none, thank you very much. I appreciate it.

Next update is from the Laboratory Standards and Procedures Workgroup. Dr. Kellie Kelm will make this presentation.

LABORATORY STANDARDS AND PROCEDURES WORKGROUP

DR. KELLIE KELM: Do I do the slides? Yes? Good. So, we had a fantastic meeting yesterday. We also had some new members join, and I didn't choose red. So, Stan Berberich and George Dizikes have returned, gotten new terms on

a workgroup, and we had two new members, Nathalie Lepage from Ontario and Miriam Schachter. And so, they were able to join us by phone, and it was great to have those two new folks. So, I included all of our --

So, one of our new projects that we had -- it's been recent -- was that the committee gave us was the impact of broad phenotypes in labs, i.e. share lessons, learn on identifying late-onset Pompe or SMA, et cetera. And so, we did have some -- number one, we had an update from APHL on the limitation of screening for new conditions, and then we had presentations from two states on screening for SMA and their experiences.

So, briefly, APHL told us about their recent activities in the New Conditions Implementation update, so they have funded sixteen states for implementation projects and three states as Peer Network Resource Centers. So, the three Peer Network Resource Centers are three states that are early adopters for screening of the three conditions. That's sort of to help

other states with questions and technical assistance, and these states include both states that do mass spec for screening and use the digital microfluidics platform. So, the great idea is that if people are bringing on the different technologies, that they can get help from these three states for either of those.

APHL also let us know that there would be a New Conditions Workgroup starting soon and that George Dizikes and Amy Gaviglio will be the co-Chairs, and they will be setting up webinars with topics of interest from the states as well as more technical assistance. APHL said that they've gotten additional funding for SMA and other disorders as they're added for the next five years. So, this type of help will be ongoing.

So then, we heard from Anne Comeau, who gave us an update on adding SMA screening in Massachusetts, and so, she had a lot of details on their first- and second-tier tests, very detailed molecular details that I would not be able to explain them, both because I would need to do --

have done some more homework last night to remind myself of molecular testing. But, obviously, I don't want to mess up any of the details that she shared. But if you have questions about their first- or second-tier tests, obviously, you can talk to Dr. Comeau. But they have an assay that they're doing just in Massachusetts. It is a single plex assay. They're doing it separately from SCID, and the only thing is that they are extracting the DNA before they are doing the molecular testing, and they're detecting homozygous absence of SMA1 exon 7, and they are not detecting carriers.

So, this is their current screening algorithm. So, they have a process for detecting babies that have in-range results, but then indeterminant tests that would need retesting, either where they need to back and get a new specimen because after a second retest, it's obvious that they will not be able to get a valid test and then those where they have moved on on the right side to retesting tier 1 and then doing

their tier 2 test.

And so, she provided a lot of details on some of the experiences and the results they've received, and I'm not going to go into that. But, as I said, you can talk to Dr. Comeau if you have any questions.

So, as of April 16th, they've screened about 70,000 babies in Massachusetts, and this is just showing you that out of the 60,000 -- 70,000, they've had 90 that have gone on and needed -- where they have done tier 2 testing; 70 percent of those have actually been NICU babies, and they had 1 that they moved forward with confirmatory testing, and I can tell you that that one was a false positive, and it appears that the specimen contained an inhibitor, and they've been doing a lot of work with that specimen to show that. So, at this point, they don't have a true positive in their screening in the past year in Massachusetts.

We then got an update from Utah. So, this is a little bit of detail on their assay.

So, they have multiplexed it with the SCID, and they -- they actually don't do a separate extraction, it's all in -- all together, and you can see that they have details here on using the Roche LightCycler and their 384 well format for testing. Let's see. So, at the beginning, their process for SMA screening and diagnostic workflow was the following. So, first screen, repeat screen, and then sending on for diagnostic testing after two abnormals. Let me see. And then SCID was similar in first screen, repeat screen, and then flow cytometry.

So, at this point, they have identified two cases, and so both of these babies had three copies of SMN2 and they have information that both of these babies have opted for the gene therapy trial.

So, here are the statistics they provided in terms of the number of repeats they've had to do. SCID was added to this -- they're giving the results just of this assay, and so the reason why SCID is less is because they added in

SCID into this assay later than SMA.

So, one of the things that he noted was they have had two false positive SCID cases. This is specifically with this new multiplexed assay. And the hypothesis is -- and apparently, they're not the only ones that have seen this -- is that now that they've multiplexed it with SMA is that it has changed the assay and that they have actually seen some issues with increased rate of false positives with the multiplexed assay.

So, what they've done in Utah is they actually had also validated the PerkinElmer EnLite TREC assay, and so for SCID, they've actually added that if they have two abnormal screens, that they'll actually go to the PerkinElmer EnLite TREC assay before they move onto flow in order to reduce the false positives. So, that's what Utah has presented as their current screening algorithm for SCID with this multiplex assay.

So, lastly, we did have a brief discussion about the discussion of the committee about the condition nomination evidence review

process, and the top two bullets are pretty much exactly what Beth Tarini said in her own blurb. So, we agree on the need to define the terminology for the evidence review process and what came up from multiple folks was that they also dislike to use the word target. So, I think there was preference for, you know, using case definition or condition, and they also agree that we have to set the case definition for the condition under consideration because while Beth said it was essential for education, for us it's essential to know what the laboratory is supposed to find.

Still having discussions about whether identifying carriers is a benefit or harm, and I know a lot of times, that really depends on your lab and your viewpoint. And what was also raised is that often we've had -- it's been very difficult to find published evidence of harm, but that doesn't mean that we shouldn't look for it.

Other concerns from the workgroup is they'd like to see a better assessment of the availability of the confirmatory test, turnaround

time, and making sure that we're getting information on how well those tests perform. And then, more information, if possible, on specialty care availability, so will we actually have the clinical experts -- will we have information on them.

And we did have one person share that you know, there are ways to measure family experiences, and it's something that we should consider, and the example given was Maslow's hierarchy of needs. And so, something to think about as we try to do an evidence review for new conditions.

So, I think that's it from us. Anyway.

DR. JOSEPH BOCCHINI: Thank you, Kellie. Questions, comments? Dr. Parisi.

DR. MELISSA PARISI: Melissa Parisi. Kellie, I have a question, and maybe this is more toward -- for Anne Comeau. But I'm wondering about the false positive rate for SMA screening in premature infants and if there's an explanation

for that. Is the source of blood coming from a central line, or something that might be contaminating or inhibiting the reaction? Do you have any thoughts?

DR. CATHARINE RILEY: Dr. Comeau, would you introduce yourself please.

DR. ANNE COMEAU: I'm sorry. Anne Comeau from Massachusetts. As noted, most of the false positives are from NICU babies, and we investigate whether or not anyone is using heparin. We are not using -- we are using an enzyme that would be more sensitive to heparin. Many people refuse -- they deny that they're using heparin. But in the one false positive that we did have, we actually were able to mix that specimen with other specimens, and we were able to dilute it out. This clearly was an inhibitor, most likely heparin.

DR. BETH TARINI: This is Beth Tarini. When they take the NICU specimens, do they take it from the heel, or do they take them from the umbilical?

DR. ANNE COMEAU: Well, they're supposed to take them from the heel. They're supposed to take them as a heel draw. That particular specimen when we called on it, they told us that no heparin, no heparin, but we used a capillary, and they were re-informed that they're not supposed to use capillaries for this. So, it's this ongoing education and, you know, everybody has a difficult thing to deal with.

But, so one last thing is that we do have a very active SCID -- SMA Working Group. Our -- the surveillance is excellent. So, I'm pretty sure that we are not missing any, but I'll knock wood on that.

DR. JOSEPH BOCCHINI: Dr. Baker.

DR. MEI BAKER: I just have a followup, because you talked about SMA and NICU babies. What's your observation for SCID?

DR. ANNE COMEAU: It's the same thing. I think it's not -- so we have -- we have our heavy-hitter hospitals that we have high suspicion use heparin quite a bit. And one SCID,

there were more, and they -- they slowed down using heparin because we told them that we were just going to keep on calling them back and asking for repeat specimens until we got a satisfactory specimen, and they didn't like that. But, with SMA, the feeling was that the turnaround time was more important, so that makes it more difficult.

DR. DEBRA FREEDENBERG: Anne, how premature were these babies? Were they near term? Were they extreme like 23 or 24 weeks?

DR. ANNE COMEAU: A wide range. There were 90 babies. It was a wide range of gestational ages there.

DR. SHAWN MCCANDLESS: Anne, while you're up there, maybe you could comment for people who've been looking at the map for the screening almost 70,000 babies for SMA and getting zero positives.

DR. ANNE COMEAU: Getting zero, yes. I'm sorry, there was a question?

DR. SHAWN MCCANDLESS: Yeah. What -- how does -- what was your expectation and what

do you think the -- what's the probability that you would screen 70,000 infants for a disease that's said to have a --

DR. ANNE COMEAU: One in ten thousand.

DR. SHAWN MCCANDLESS: One in ten thousand and not get any positives.

DR. ANNE COMEAU: Yeah, pretty low, and when we got to about 30,000, I started having nightmares. Every single one of those has been sequenced, so we know that every single one of the 90 presumptive positives that went on has been sequenced. My speculation with very limited evidence is that Massachusetts has a quite active prenatal and preconceptual offering of the Council Panel of Disorders and SMA and Pompe are on that Panel as I understand it MPS1 is not, and this year, we went forward with screening for four conditions, and the Pompe, which is lower anyway, but Pompe and SMA are way lower than the disorders that we think are not on those panels.

DR. SHAWN MCCANDLESS: That would be

a really nice publication if that's true to confirm.

DR. ANNE COMEAU: Yeah, I have no way of proving it though.

DR. SHAWN MCCANDLESS: To confirm the value of carrier screening, which many people suspect is not going to be an effective way of screening and really this would suggest it could be.

DR. ANNE COMEAU: It's very important. Thank you. It's very important. We actually saw this with CF when we -- we're on 20 years of screening for CF and when we first started, we were getting 30 babies a year, and right about the time that the -- the prenatal testing was offered, 30 babies dropped to 15 babies a year, and the 15 babies that were missing were the Delta 508 homozygotes. We published -- we published that. That was really good solid evidence-based information. I don't have the evidence base for the prenatal testing of this. It would be wonderful though and thanks.

DR. SHAWN MCCANDLESS: Thank you.

DR. JOSEPH BOCCHINI: All right. Any additional questions or comments for Dr. Kelm? On the telephone? All right. Hearing none, thank you very much. Thank you.

RUSP CONDITION NOMINATION AND EVIDENCE REVIEW PROCESS: FOLLOWUP DISCUSSION

DR. JOSEPH BOCCHINI: All right. Next on the agenda we put a few minutes for any further discussion that the committee might have or organizational representatives related to Dr. Kemper's presentation yesterday and Dr. Powell's discussion, and then now, after the couple of workgroups have had the opportunity to really discuss some of the issues that were presented, is there further -- and you've all had a chance to think about this -- is there any -- are there any further comments, questions that -- that might be directed toward the review, and how to go forward with additional things? I think the two workgroups that had a chance to discuss some of what was presented have given back some feedback

that would be helpful to Dr. Kemper, and the -- his group. Any other comments or questions? Yes, Annamarie.

MS. ANNAMARIE SAARINEN: I don't -- okay, now it's working. I'm just moving a little closer to it. What has been done historically either out of this committee or handed off to someone else with regard to newborn blood spot screening in the NICU? I am sorry that that spun out of that thing, but I'm just like, you've got to be kidding me that, you know, there's blood being taken from different sources and obviously, that's going to have an impact, and I can see spending a lot of time in NICUs, I can totally see how that would happen. But I just -- I don't -- I don't know what's -- what's been done so far, and I would really like to encourage those of us who are in that space to take -- I would be more than happy to dig into that a little bit with our NICU projects and try to learn more about what's happening and how the education resources may not be reaching them or there's something that's still

needed.

And then, while I have the microphone, since I didn't say thank you and congratulations yesterday, I will do that on the public record. Thank you for your leadership and your service. It's been a privilege.

DR. JOSEPH BOCCHINI: Thank you, Annamarie. That is a really good question, and I'm not aware of what's been done or what the current status of that is, and that might be something that -- Kellie, you've got some information?

DR. KELLIE KELM: Well, one of the things with timeliness is we did sort of talk about whether or not we can move forward, because that was something that we heard a lot was education of the nurses, a lot of turnover in the hospitals, you know, with unsatisfactory specimens, not even touching on the NICU. And so, then there was some discussion could we talk to the Joint Commission about adding a standard. We tried to reach out to them, and they weren't very

receptive. And so, that is an issue.

I'll also share that I know that having served on the CLSI document for, you know, blood collection, that has a lot of that information, and I know a lot of folks, it's one of their most purchased ones. They have videos, they have everything, you know, they're trying to work on so many different ways to provide all that information in a way that's even, you know, they talk about whether or not we can do it on apps or something like that. But, you know, what is a way, you know, and I think that's already information that's already being put together by experts that could be shared, and I think that's one of the questions. So, I'm not sure how we could do it better. I mean, we've had a lot of discussion about that and how we could -- we could do that, but I think that's been a struggle.

And a question about time and effort of the committee and figuring out how best we could do that, so.

DR. JOSEPH BOCCHINI: And that

certainly can be a topic that Dr. Powell considers going forward. I'm trying to be good. All right. Other questions or comments? Natasha.

MS. NATASHA BONHOMME: Natasha Bonhomme, Genetic Alliance. I was just going to add to that. One thing that we saw, and this is not just in NICU but in working nurses in general, is sometimes even hearing what you're supposed to do is not as effective as hearing what happens when you don't do it right, like kind of what are the outcomes. So, I think even if -- and I haven't seen the CLSI materials -- but without that piece, then it's -- it makes a difference from someone thinking that oh, this is a preference to oh, if I do it this way, there's actual consequences that I may not see, but will affect this baby. So, that's just something else to be thinking about when thinking about the educational components. It's not just the methodology, but really highlighting why it's a no, like why we don't want to use a particular procedure.

DR. JOSEPH BOCCHINI: That's a good -- good point. Melissa.

DR. MELISSA PARISI: Melissa Parisi, NIH. I just noticed from the comments made from the public commentary that some issues were raised about both homocystinuria and CAH, and I know in the past, we've had opportunities to sort of discuss issues that may arise with existing screening and potentially need for re-examining the methodology that's used, and so I just wanted to raise those two to the level of potential consideration for a future meeting. I know we did the same, I think, for succinyl acetone and tyrosinemia, and so this would be -- these two would be other examples. Thank you.

DR. JOSEPH BOCCHINI: Perfect. Thank you. Mei.

DR. MEI BAKER: Yeah, I just want to follow Melissa's comments, actually on CAH is making me thinking. The public comments mentioned that false positive and I think that a lot of states have second-tier -- use a sterile profile

for the second-tier, and that's helped with sorting out the 17-OHP elevation is truly a deficiency at all, because most of the NICU babies there have this stress. But I recently learned at an APHL meeting, Kiki from Minnesota did a very good presentation. Actually, CAH is challenging not only false positive but also false negative, and the false negative -- when you have both and you have a different way to dealing with it. Actually, personally I was looking more into CDC has done a very good job of working with Minnesota to develop an assay to do the more legal part, and that can -- that probably should be taken into consideration too.

DR. JOSEPH BOCCHINI: Thank you. Other questions or comments? On the telephone? Okay. Thank you all very much for the input.

So, as we're nearing the end of the second day of this meeting and we're in the middle of a Chair transition, Dr. Powell would like to come forward and talk about her vision for moving this committee forward. And so, we've given her

time on the agenda, and she's titled her presentation On the Horizon. Cindy.

ON THE HORIZON

DR. CYNTHIA POWELL: Thank you, Dr. Bocchini. So, I'd like to spend a little bit of time just reviewing the last charter for this committee, and forgive me for reading the objective and scope, but I think it's a helpful reminder for all of us of what our -- our objectives are.

So, the committee provides advice, recommendations, and technical information about aspects of heritable disorders and newborn and childhood screening to the Secretary of HHS for the development of policies and priorities that will enhance the ability of the state and local health agencies to provide for such screening, counseling, and health care services for newborns and children having or at risk for heritable disorders.

The duties include making a systematic evidence-based and peer-reviewed

recommendations, providing technical assistance to individuals and organizations regarding the submission of nominations to the Uniform Screening Panel, developing a model decision matrix for newborn screening expansion, including an evaluation of the potential public health impact, including the costs of such expansion, and periodically update the Recommended Uniform Screening Panel as appropriate based on such decision matrix.

And I think our current process, which will be ongoing of reviewing the nomination and evidence review is extremely important and how we can look at improving the process and helping those who wish to nominate conditions.

We also consider ways to ensure that all states attain the capacity to screen for the conditions that are recommended to the RUSP and certainly the funding that comes from the -- the CDC and HRSA and NIH that can help with that is extremely important.

We provide recommendations, advice,

or information as may be necessary to enhance, expand, or improve the ability of the Secretary to reduce the mortality or morbidity from heritable disorders.

And, as you know, we have several standing workgroups whose Chairs or co-Chairs presented to us, and there are workgroup charges, and I thought looking briefly at what those charges are.

For the education and training workgroup, they are to review existing educational and training resources and to identify gaps and make recommendations regarding the following five groups: health professionals, parents, screening program staff, hospital/birthing facility staff, and the public.

For the Followup and Treatment workgroup, to identify barriers, to post screening implementation and short- and long-term followup, including treatment relevant to newborn screening results; to develop recommendations for overcoming identified barriers in order to improve

implementation, and short- and long-term followup, including treatment relevant to newborn screening results; and to offer guidance on the responsibility for post-screening implementation and short- and long-term followup, including treatment relevant to newborn screening results.

And finally for Laboratory Standards and Procedures, to define and implement a mechanism for the periodic review and assessment of the conditions including in the uniform panel; the infrastructure and services needed for effective and efficient screening of the conditions on the panel; and laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel.

So, as you know, we also have Ad-hoc Workgroups, currently the one interpreting newborn screening results led by Dr. Baker, and I think going forward, thinking about, you know, is the current charge and scope of the workgroups meeting the needs of the committee? Are they adequate to address current and future needs? And I think

going through a similar process that was done initially at the formation of the workgroups may be helpful to get information and feedback back from the workgroup members as well as the committee members in terms of are there other needs that aren't being addressed? Is there a need for any other Ad-hoc workgroups? Is expanding the scope of the current workgroups appropriate? Specifically, for the Education and Training Workgroup, which I've been serving on and Dr. Tarini told us today that, you know, we've completed products and are really ready to take on other initiatives and other, you know, procedures in order to go forward with that, so, an opportunity there.

Transparency is certainly an important aspect of what we do. Based on the requirements of FACA, certainly transparency in terms of the public nature of the committee meetings and the opportunities available for the public to present their views, I think in the future if we can have more time perhaps for

additional comments from the public, you know, knowing that there are some time constraints with our meeting schedule, but that that would be helpful.

And I also think that on the part of organizations and experts who are nominating conditions for us to consider, that improving the transparency would be very helpful and to have more information regarding outcomes instead of having to go through the -- the gray literature that's out there, ideally having more publications in peer-reviewed journals for us to consider when we're -- we're going through the evidence-based reviews would be extremely helpful.

So, there's many challenges. As we heard at our -- our online meeting last month, there are 7,000 rare disorders out there. Only about 5 percent of them currently have treatments available. It's been estimated that there are about 450 medicines in development to treat rare disorders, and often pre-symptomatic treatment is superior. Early diagnosis is important, and, you

know, I -- my belief is that there will be an accelerated pace of conditions that are submitted for nomination, and one of the challenges of our committee is how to keep up with the volume while maintaining a thorough evidence-based review and some ideas that have been suggested about that are to look at, you know, panels of conditions or groups of conditions versus individual conditions. So, will we -- I don't have an answer to this -- but will we need to have a high-throughput review process?

And, as we've heard today about registries and really, you know, excellent registries that are out there, but I think we're only going to be able to look at the long-term outcomes of newborn screening conditions in patients if we have registries that are easily accessible, that are maintained long-term, and, you know, if I had my ideal situation with all the resources available to have single registries that would -- a single registry that would include all rare conditions, especially those that we're doing

newborn screening for, and long-term followup. So, to have input both from clinicians as well as families. We want as accurate clinical information as possible, but we also want to learn about family experiences, what they're going through with, you know, having a child who has screened positive, especially with more and more of the conditions that are included on the panel where the majority have late-onset and some may have, you know, no -- no onset of the disorder -- we know such as for X-ALD, for example. So, how do we provide appropriate long-term followup for these conditions, support families, keep track of families as they move from one state or region to another? So, these registries are very important in the work of this committee to investigate and hopefully make recommendations in the future about what we can do to have states be able to be supportive in their -- their registries.

You know, we know that California has done an excellent job in following children for at least the first five years of life. And, you

know, we've seen the benefits from registries in terms of what's been done for childhood cancer, and it's only been from the data that they've been able to collect and share that the survival rate for childhood cancers has increased greatly in the last 20 to 30 years.

So, I wanted to talk about timing, not in terms of timeliness of getting those dried blood spot cards into the state labs, but to think about timing of newborn screening. And, you know, we know that there are conditions with onset in the newborn period, for which our newborn screening results come too late. And would there be, you know, benefit in screening in the prenatal stage -- so, what I'm calling prenatal newborn screening. Examples of these conditions are urea cycle disorders, you know, we know that often with OTC deficiency, babies crash, you know, have severe metabolic crisis before the newborn screening results come in, even when they've, you know, collection has been timely, the laboratory reports them out quickly, but the hyperammonemia

comes on and it often causes severe brain damage before we, you know, know what the condition is from the newborn screen. That also can use examples of some of the organic acidemias, fatty acid oxidation disorders, that also can -- can present that way. We know that breastfed babies, often the first infant born to a mother who is breastfeeding, they're discharged at 24 to 48 hours, and, you know, they aren’t getting enough intake, and have severe hypoglycemia, suffer brain damage before we get those newborn screen results.

Also, we know that there are some conditions that likely already begin in utero. One of the reasons that's been hypothesized for the not-ideal-outcomes for children of Krabbe disease who are diagnosed through -- in some states through newborn screening is that the process starts in utero. Also, in the most severe form of spinal muscular atrophy or type 0, those motor neurons have begun to die prior to the infant being born.

And at the last ACMG meeting, there

was a session about prenatal treatment for genetic disorders and from the right side of the slide, using maternal stem cells to treat the fetus and do stem cell therapy in utero is still at an experimental stage but having some success. The engraftment is improved, and this is being done -- studies are ongoing for hemophilia A, immunodeficiency alpha thalassemia. There is certainly risk that has to be considered to the other, the fetus, or the fetal germline, but, you know, things are progressing in that area. So, another reason that doing screening on the -- the fetus at an earlier stage, prior to birth, may be something to consider.

And then, in the upper left are two twin brothers who were treated in utero for X-linked hypohidrotic ectodermal dysplasia, a condition where children do not sweat, and so they can't be in a hot environment. They'll suffer heat stroke easily unless they're wearing a cooling vest. And anyway, these little boys were treated through using the protein product that's

deficient in this condition during the second and third trimesters of their mom's pregnancy with them, and they actually grew sweat glands and are now able to function quite normally outside, whereas their older brother who was not treated has severe classic type of ectodermal dysplasia, very heat-sensitive. It remains to be seen whether it's going to improve the dental development, which is also a problem, but not nearly as life-threatening a problem as the lack of sweating is.

There are also conditions for which later detection may be sufficient and perhaps more appropriate. However, and I think this committee in the past has kind of looked at the possibility of a later-in-childhood screening, but I think the challenge of this is to make it accessible for everybody and to avoid health disparities.

So, I've used this slide for many years in teaching our residents and other physicians about newborn screening, and I think I don't have to explain it much for most of you in

here, who are aware of the short-term followup, but then the very long period of long-term followup that's needed for conditions that we screen for in newborns. So, when we, you know, have an infant who screens positive, we do confirmatory testing, we confirm the diagnosis, we institute therapy, and then it can be a lifetime -- decades of long-term followup. And as the doctor who started my Division of Genetics and Metabolism at UNC used to say, "If we don't provide treatment for women who are pregnant with PKU, all the newborn screening in the world is for naught." So, we have to think about that again with especially these conditions that have adult-onset.

And the complex newborn screening system, it's not just the state laboratories -- although their critical -- but the need for a medical home, consideration of the family, the specialist medical services, as Dr. Watson mentioned earlier, the shortage of specialist providers, and it's not just in genetics. It's

also for pediatric neurologist and pediatric endocrinologists. There's a severe nationwide shortage of pediatric specialist providers. Thinking about the community resources available, therapy services, insurance and Medicaid coverage. In my state, Medicaid will not cover for any genetic testing, so that if we don't do that genetic testing as part of the newborn screening, we're not going to be able to order testing or my hospital won't be reimbursed -- it's not that we don't order it and try to slip under the radar so the hospital administration doesn't get on us for, you know, having these unreimbursed expenses -- but anyway, I think that's something we have to think about when so much of the second- and third-tier or confirmatory testing involves genetic testing, sequencing or even targeted genetic testing and how are we going to make sure that that gets done, available to everybody and paid for.

And then, the others involved in the newborn screening process are genetic counselors,

metabolic dieticians and nurses, and then the complex therapeutics. It's much more than a specialized diet. We're now dealing with intrathecal therapy, very expensive therapies, stem cell therapies, gene therapy, et cetera.

So, there's a lot of things to balance out in this, and we have our advocacy groups and new treatments, new conditions. Two or three times I get an alert about a new genetic cause that's been identified for a rear condition. We have new screening methods being developed. But we also have to consider the health care costs, the impact on the newborn screening system, the ethical issues involved, equal access to care, evidence-based reviews, pilot studies, data, long-term outcomes, and at the foundation is research, and not just basic science research but translational research and also funding for, you know, very important pilot studies, and as I've already talked about, for the registries.

So, we're in the world of genomics. We hope to have another presentation in the future

from some of the EnSight Groups. We heard from those involved in the Ethical Studies of the EnSight projects, which we're looking at the utility of the use of genomic sequencing in newborns, and we hope in the future to hear about some of those projects that are now being completed.

We have, you know, fascinating work being done for new treatments, new screening methods. I think at our last meeting, I think, it was Dr. Ostrander who brought up about direct-to-consumer testing, and that's something that's here now. I am reminded of the -- the work or the direct-to-consumer push that was done for tandem mass spec back when that was just getting started, and it was being offered to families. Often grandparents would purchase it for their -- their grandchildren to get the tandem mass spec. This was before the vast majority of states were offering it. I think it did move things forward, so maybe that is a way potentially, you know, to move this forward and to give us more data about

the use of some genomic testing as part of an expanded newborn screening.

So, I'm taking advice from my cousins in the UK and also from Hippocrates. So, keep calm, and first do no harm. So, I think on the horizon, the horizon is bright. There's a bright star on the horizon. It's an exciting time. It's very challenging. I will say that specifically for -- on the horizon, we do plan to have a presentation at the August meeting from the CDC about their work, looking at the challenges of homocystinuria newborn screening and, you know, looking at the high false-negative rate for homocystinuria and ways that that might be improved. We've asked Dr. Kelm and the Laboratory Workgroup to begin to look at this area and hopefully make some recommendations to the committee at an upcoming meeting.

Finally, I'd must like to acknowledge again Dr. Bocchini and his, you know, just support and guidance to make this transition as smooth as possible, and again thank him for all he's done.

To Dr. Howell, who has always been a source of historical information and support and guidance, and hopefully we'll continue to work together over the years.

Dr. Dianne Frazier, who's now retired but one of my dear friends and colleagues who taught me a great deal about newborn screening in North Carolina.

And Dr. Kirkman, who I mentioned earlier, who helped get newborn screening started in North Carolina and started our division.

Dr. Don Bailey is the -- he's a mentor of mine, somebody I've worked with for many years on various projects and has been a member of this committee in the past. Thank him for his support.

To my fellow committee members, our organizational representatives, our workgroup members, the HRSA administration and staff, Dr. Warren, Joan Scott, Dr. Catharine Riley, Debi Sarkar, Alaina Harris, and Jill Shugar, who I've known since I was a genetic counselor at

Children's National, and Jill was in charge of the DC Newborn Screening Program. I won't tell you how many years ago that was. But anyway, I think Jill was the first person, who a few years ago said to me, you should -- you should put in an application to serve on that committee. So, I do still thank Jill for that. And I'd also like to thank NIH. So, thank you all.

DR. JOSEPH BOCCHINI: So, it's very clear that this committee will be in excellent hands as we make the transition. So, thank you Cindy. I think it's very clear from your presentation that you have the skills and the commitment to make this committee move forward in an excellent way. And I think you're very well positioned. I think we have two new excellent members on the committee. Each of the workgroups welcome a series of new participants, new members of each of the workgroups that were added at this meeting, and in August, you're going to have two new organizations that will have representatives here at this meeting. All these will strengthen

the activities of the committee and make you have the opportunity to continue the success that the success that this committee has had.

I said all of my thank you's yesterday. I just want to repeat what an incredible experience this has been for me and what an opportunity you've all given me to participate in what I think is one of the finest committees in terms of what we all do to help infants and children in the United States and it's very clear from some of the presentations even today how successful the recommendations of this committee have been to improve the outcomes for infants and children and their families. So, I'm very pleased to have had a small part in that.

So, as Dr. Powell presented to me as we made the transition a virtual gavel, I will do the same to Dr. Powell. I will give to you [speaking off mic]. That's two microphones down, so I -- or maybe that's a sign from HRSA, I don't know. It's time for everybody to leave. So, I want to thank HRSA particularly. You all know

that we -- we had a meeting last month, and so within a one-month period of time, they were able to put together another highly successful meeting, and that goes to the professionalism and their commitment of all of the people at HRSA to make this possible. So, again, this is a great group that supports the work of this committee and has made the committee quite successful. So, thank you all very much. So, with that, I'll conclude before this microphone dies. Thank you all very much. Appreciate it.

[Whereupon the meeting was adjourned.]