The Advisory Committee on Heritable Disorders in Newborns and Children

HRSA Meeting

HRSA HEADQUARTERS

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A P P E A R A N C E S

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C O N T E N T S

P R O C E E D I N G S

Welcome, everyone to day two of our Advisory Committee on Heritable Disorders in Newborns and Children, November meeting.

So I'd like to welcome you all back for today, and we're going to start today's session with the roll call.

So Kamila Mistry.

(No audible response)

She might. She should be on phone this morning. Is the phone open?

DR. KAMILA MISTRY: Yes. Can you hear me?

DR. JOSEPH BOCCHINI: Yes. I can now. Thank you.

DR. KAMILA MISTRY: Great. Thank you.

DR. JOSEPH BOCCHINI: Mei Baker.

(No audible response)

Okay. Still coming.

Sue Berry.

DR. SUSAN BERRY: I'm here.

DR. JOSEPH BOCCHINI: I'm here.

Jeff Brosco.

DR. JEFFREY P. BROSCO: Here.

DR. JOSEPH BOCCHINI: Carla Cuthbert.

DR. CARLA CUTHBERT: Here.

DR. JOSEPH BOCCHINI: Kelli Kelm.

DR. KELLIE B. 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 M. SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini.

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: And Catharine

Riley.

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: Organizational representatives.

Bob 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 Rink by webcast.

DR. BRITTON RINK: Here.

DR. JOSEPH BOCCHINI: Jed Miller by webcast.

DR. JED MILLER: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley.

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus by webcast

DR. CHRIS KUS: Here.

DR. JOSEPH BOCCHINI: Natasha Bonhomme.

(No audible response)

DR. JOSEPH BOCCHINI: Siobhan Dolan by webcast.

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: Cate Walsh Vockley.

DR. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: And Shawn McCandless.

DR. SHAWN MCCANDLESS: Here.

DR. JOSEPH BOCCHINI: All right. Thank you all very much.

So to start this morning, we do have one public comment before we get into today's scheduled agenda. Mr. Ron Bartek from the ALD Foundation is going to give us a brief update on the newborn screening roundtable that was held, oh, just prior to our meeting.

DR. RON BARTEK: So thank you, Dr. Bocchini and Committee members for the opportunity to give you a brief report on what we

did on Wednesday in the RUSP roundtable discussion.

We, as usual, discussed a broad range of perspectives coming from the various representatives, including the state lab directors, pharma, clinical care expertise, policy and legislation, patient advocacy, and pertinent technologies.

Unfortunately, the RUSP roundtable organizer and facilitator, Dean Suhr, was unable to make it today. He's up in Philadelphia on a different commitment, so was unable to share this update himself.

Our discussions ranged across a wide spectrum of issues. One set of such issues dealt with various aspects of the tensions between the state labs and the federal committees process and recommendations. This discussion centered on what should be or could be considered the optimal level of certainty that mandated screening of a condition will result in sufficient benefit.

Recognizing that such certainty is especially difficult to obtain for conditions for which diagnosis did not occur until symptoms are clinically manifest, and a great deal of damage is already done, or for which later onset of symptoms occurs, the group discussed how research screening protocols could be needed to achieve such certainty in these circumstances.

Another aspect of tension between the state and federal processes we discussed was the delays in state decision-making and implementation. One roundtable participant believes that these delays are far more the result of this kind of tension between certainty and uncertainty than from any concerns about funding levels.

The group was also briefed on and discussed the efforts of private providers of pre- and postnatal screening options for diseases not currently screened for in the various states.

We also received a briefing on current

efforts regarding reauthorization that of the Newborn Screening Saves Lives Act and the possibility that this reauthorization might include additional funding, and if so, for what particular aspects of newborn screening that additional funding might be applied.

Finally, the roundtable discussed the clear need to think outside the box, given the fact that we believe that newborn screening might look completely different in five years' time.

For example, we considered briefly how new technologies and the potential for regenerative medicine, such as gene therapy, might drive new considerations for newborn screening across the board.

Our next meeting will be adjacent to the Committee's meeting in April, and our focus at that point will be on several topics. One would be this idea that newborn screening is likely to change drastically in five years' time; what might it look like; and how might we

strategically work to get there; and finally, concerns about long-term follow-up issues and shared experiences.

Finally, I'd like to invite everyone to visit newbornscreening.us, where we will have a report written up on the roundtable meeting by next week. So thank you very much.

DR. JOSEPH BOCCHINI: Thank you, Mr. Bartek.

So first item on our agenda for today is a panel on genomic sequencing and newborn screening -- ethical, legal, and social implications. So we're very pleased to have this panel of experts in this field. The panel will focus on all of these considerations related to genomic sequencing in newborns. This is a very timely topic for the Committee, with the August 2018 publication of the special report from the Hastings Center, in collaboration with the University of California, San Francisco's NSIGHT Ethics, and Policy Advisory Board.

This report, "The Ethics of Sequencing Newborns: Reflections and Recommendations," is a compilation of articles on a variety of topics related to sequencing in the context of newborn screening and in the clinical setting for both well and sick babies.

We've heard from a variety of speakers over the past few years regarding emerging technology and the application of genomic sequencing, and the Laboratory Workgroup has been following this topic closely.

We hope the panel today will generate discussion about benefits, challenges, and possible next steps for the Committee.

Dr. Cindy Powell, Committee member and co-chair of the Education and Training Workgroup, will provide introduction to the genomic sequencing and newborn screening topic, and then introduce her esteemed panel members, who will then share their expertise with us.

So Dr. Powell.

DR. CYNTHIA POWELL: Thanks.

Thank you, Dr. Bocchini. Thank you, fellow Committee members and guests. We're happy to be able to present some information from the NSIGHT projects today. As Dr. Bocchini said, we've presented the early phase of our projects, and hope to present more of the clinical information in the future as we finish things up.

So this morning, I was asked to give a little bit of information about genomic sequencing. I know many of you are experts in this area, but some of you may not be that familiar with how this done and why this is done. And I wanted to give a bit about the background of the NSIGHT program, an overview of the four NSIGHT projects, and then introduce the speakers.

So what is our genome? Well, our genome is within the nucleated cells of our body and arranged into condensed bodies called chromosomes. And if we were to stretch out the chromosomes, you'd see the long stretches of the

double helix that we're familiar with.

And this is how our genes are arranged. And one important concept is that genes code for proteins; at least a good number of our genes code for proteins. And proteins can act alone or in complexes and things that carry out many different functions in our body.

Another important thing is to know that DNA is made up of nucleotides. And these are molecules, and you can think of them as letters -- A, C, T, and G -- standing for adenine, thymine, cytosine, and guanine. And each nucleotide has its corresponding partner, and the two of these together are referred to as base pairs.

So a gene is made up of thousands of nucleotides, or base pairs. Some genes are fairly small, as small as 250 base pairs; others are very large, as large as 2.5 million base pairs. But we can think of it as these letters of the alphabet arranged sequentially.

Now, when we think about differences -- and all of us have differences in our DNA sequence. Let's consider one change in one nucleotide, cytosine in this case. So what happens if we were to change the C to a T? Does that make any difference?

And that's one of the big areas that we focus a lot of our time on when we look at someone's sequence is what is a significant change -- what we would term a mutation, or a pathogenic change -- and what's just a benign change, because by far, most of our changes are just benign variations.

So what types of variants can we run across? Some of these are point mutations -- as I gave the example, a T instead of a C. Some are deletions, where that nucleotide is missing. Others are insertions, where there's extra material inserted into the DNA sequence.

So you can think of it as letters in a sentence -- in this case, the example being "The

cat saw the dog," if we say that's the normal sequence. Well, if we change a C with a B, that would change the meaning of the sentence, right -- "The bat saw the dog." So that would be, essentially, an example of a point mutation. If we were to delete a whole word, it could say "The cat, the dog" -- again, not very meaningful. If we inserted a letter, "The cart saw the dog," again, it would change the meaning of the sentence. And then we know that there are some variations in our DNA that create extra repeats of DNA sequence. So we'd say, "The cat saw, saw, saw the dog" -- again, would change the meaning.

But instead of changing an important letter in a word, what if we were to just put a K instead of a C? So it would still say "The cat saw the dog" -- so a fairly benign change.

So how do we go about looking at our genome? Since the 1800s, we've known that looking under a microscope, we're able to see our structures, called chromosomes. And in the

1950s, it was discovered that humans have 46 chromosomes, or 23 pairs of chromosomes.

And for a long time, that was essentially how we looked at the whole genome. But granted, it wasn't a very detailed way to look at it. But we're able to look under a microscope, count the number of chromosomes, see if there's an extra chromosome, such as we see with an extra 21 chromosome in individuals with Down syndrome.

So each chromosome contains from 50 to 250 million nucleotides. And at best, we're able to get down to about a four million base pair of region that we're able to see under the microscope. So, still, a lot of things can be changed in our genome that we're not able to see with that technology.

So it's kind of like thinking of a Google view of the Earth, where we might be able to look at a neighborhood, and we could see, you know, the number of houses on a street and maybe a little bit more detail in the neighborhood, but

we really can't see very detailed information through that.

So tools that we're able to sequence the genome have been developed over the last 25, 30 years. So they're able to look at each one of those nucleotides and see if there's an A, T, C, or G present. And one of the original types of this sequencing was discovered by Dr. Sanger, and so you'll often hear the term "Sanger sequencing," and that's often what's called "first-generation sequencing." There's other types of sequencing methods that have been found.

So I like to use the example -- it's kind of like now we're able to not only see that whole neighborhood, but we're able to look at a letter that's present in our mailbox and see, you know, the word or words in that letter.

However, we're really, with Sanger sequencing, just looking at a single gene, because generally, from 100 to 800 or so based pairs would be sequenced. We can also do

targeted mutation analysis through Sanger sequencing. And it's still really considered the gold standard for sequencing and finding pathogenic variants or any types of change in a gene.

Now, this would contrast to what we call whole-exome sequencing and whole-genome sequencing -- and I'll just use the term "genomic sequencing" -- where we can look at 30 million base pairs in the exome, or 3 billion in the entire genome. We can look for many different target areas, but there are certainly difficulties with interpretation.

So I like to give the example that this is like having the whole encyclopedia -- if we still had encyclopedias around -- and being able to read each single page in that whole encyclopedia.

It's relatively simple. All you need is a sample of DNA. You could get that from a blood sample; you could get it from a cheek swab,

saliva sample. Really, anything that would give you tissue from the person, you'd be able to extra that DNA and do sequencing. Sequencers, you know, fit on top of a lab bench; they're not that large. But really, the variant calling and interpretation takes very high-level bioinformatics computing abilities.

And even with that, even when our computer tells us, you know, here are the variants in this individual, and they will give us a letter grade -- like is that an A, meaning that it's quite likely to be clinically significant; or is it a C, D, so very unlikely to be significant. But we still have to go through each of those individually if it's in the gene of interest to determine whether or not it's significant And at least for our project, what we do is, if we think that something is significant, we always confirm it in our CLIA molecular lab in the hospital before we report it back to a patient. So that can take several hours of

analyst time and, you know, going through that.

So, as I said, we could do a whole genome sequencing, looking for mutations in all the genes, or just the coding parts of genes, the exons. But the analysis is very complex. There are projects such as ClinVar and other projects that are trying to sort through what variants are pathogenic or not, but we still have a long way to go with that.

And in addition, there are many ethical issues about which genes should we be looking at. Should we look at all genes? Should we just look at certain lists of genes associated with various conditions, or so on, and what information should be returned to patients?

So a workshop was held in 2010 with individuals from NICHD, NHTRI, the Office of Rare Disease Research, and invited guests, and they noted that this new, sophisticated, increasingly cost-effective techniques for DNA-based sequencing may make it possible to expand newborn

screening in the future and substantially expand its clinical and public health value to identify elements of a trans-NIH research agenda that could inform the possible application of new genomic concepts and technologies to newborn screening and child health. And that's the URL for those of you who are interested in looking at the full content of that meeting.

As a result of that, an RFA was issued in August of 2012, soliciting applications to look at certain questions:

Disorders currently screened for in newborns;

How can genomic sequencing replicate or augment current technology;

What knowledge about conditions that we can't currently screen for could we learn about through genomic sequencing; and

What additional clinical information could we learn that would be relevant to the clinical care of newborns.

And there had to be three components of all of these projects: First, a large genomic data set; second, clinical research; and third, evaluation of the ethical, legal, and social implications of the possible implementation of genomic sequencing.

So, as I said, three components were required, and today we're really going to focus on the ethical, legal, and social implications in each of the four sites that have had this -- these projects have had an ELSI component.

These were the four institutions or groups awarded the projects: Robert Green and Alan Beggs, PIs at Brigham and Women's and Boston Children's; Stephen Kingsmore, who, when the project began, he was at Children's Mercy Hospital in Kansas City, now at Rady Children's in San Diego; Jennifer Puck, Barbara Koenig, Pui-Yan Kwok, who are the University of California, San Francisco; and then, my co-PI, Jonathan Berg and I, at UNC, Chapel Hill.

The Boston project has looked at two different groups of patients. One group are healthy newborns born at Brigham and Women's Hospital and whose parents are recruited after giving birth to the infant. And then they also included babies in the NICU, so critically ill newborns, in their project.

The Children's Mercy-Rady Children's group really focused on the speed of sequencing in terms of the clinical aspects, because in reality, if you order a whole exome sequence on a patience on a clinical basis, it can take anywhere from 6 to 12 weeks to get those results back. So clearly, if we were going to utilize this technology in newborn screening, it would have to be much faster than that. As well if we were going to use it for critically ill newborns, it would need to be much faster turnaround time.

And Stephen Kingsmore won an award as having the quickest turnaround time of -- I think it's less than 24 hours now that he's been able

to do sequencing. I think that's the Guinness Book of World Records that he holds in that area. And again, their groups have focused in critically ill newborns.

And then in San Francisco, they utilized dried blood spots from anonymized patients known to have metabolic conditions identified through standard newborn screening. And also, because of the work of Jennifer Puck, an expert in immunodeficiency conditions, they're looking at selected immunodeficiency genes in patients who have disorders of immune function, but were not detected through traditional newborn screening. And also wanted to look at how next-generation sequencing would enhance, challenge, or transform traditional state-mandated newborn screening.

And then our project at UNC used cohorts of patients with known conditions, and then those healthy newborns whose parents were recruited during their pregnancy. And we look at over 450 genes that we call part of the next-generation

sequencing newborn screening group. And these are childhood-onset, medically actionable. And we've also been interested in how parents think about and make decisions about sequencing their child's genomes. And as I said, hopefully, in the future, we'll have a chance to give you more information about that.

So while this was going on, in 2014 Dr. Collins, head of NIH, had an op-ed in The Wall Street Journal and said that over the course of the next few decades, the availability of cheap, efficient DNA-sequencing technology will lead to a medical landscape in which each baby's genome is sequenced, and that information is used to shape a lifetime of personalized strategies for disease prevention, detection, and treatment.

So the ELSI components of the project at UCSF has led to a project that you're going to now hear more about that looked at "The Ethics of Sequencing Newborns: Reflections and Recommendations," and in collaboration with

individuals from the Hastings Center in New York.

So our guest speakers today are Josephine Johnston, who's the director of research and a research scholar at the Hastings Center. She works on a wide range of ethical, legal, and policy issues in science and medicine, including issues of reproduction and parenting, genetics, gene editing, psychiatry, neuroscience, and the conduct of biomedical research.

John Lantos is Professor of Pediatrics at the University of Missouri at Kansas City and the Director of the Children's Mercy Hospital Bioethics Center.

Barbara Koenig is a Professor of Bioethics and Medical Anthropology at UCSF. She's the Director of the UCSF Program in Bioethics, which spans ethics research, clinical ethics, and education across the university's four professional schools.

And I think our first speaker will be -- Dr. Koenig? Okay.

DR. BARBARA KOENIG: So this actually said University of Iowa, but I changed it. I was at Mayo Clinic for a while, so just a stone's throw away. But I'm definitely now back at UCSF.

So Josephine Johnston and I are going to co-present. I'm going to start out by telling you a bit about how we came to the project that we did. And as you can see, the overall title: "Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies."

And I have a copy of our report here. You all received information about how to get it. It's actually freely available via a PDF, easy to download. So we hope you'll be able to look at it.

We have no conflicts of interest.

So I'm going to tell you just about the project, how it was set up. So, as Dr. Powell just described, we all had to have these three-part projects: A sequencing project, a clinical project, and an ethics project.

So at UCSF, we decided to have our aim for -- our ELSI aim -- be about creating a local group to reflect with experts on the ethics of newborn screening, because we're the one project that actually worked very closely with our state newborn screening project in California.

So we got the idea to get some additional funding, which we were thankful to Melissa Parisi and others at NICHD to help us with. So we basically got together the ethics experts from all four of the NSIGHT teams, as well as selected individuals from around the country, to meet together and to think about whole-genome analysis in newborns.

And we thought of this as an example of embedded ethics, meaning that we were an ethics team that was embedded with these projects that were actually working on the science.

So we created the NSIGHT Ethics and Policy Advisory Board. And the membership of that group is up on the screen. You can see a

picture of us meeting at the Hastings Center on the right. A number of the individuals who participated are on your Committee or in the audience today.

So this was our time line. We had three meetings over three years. We met twice at the Hastings Center and once at UCSF in San Francisco. We tried to have the weather guide where we met, which was useful.

Then we workshopped the draft analysis and recommendations at several places and several meetings around the country, including the June 2017 ELSI Congress, which is an important meeting.

And then we created this final publication with some recommendations, plus 12 accompanying essays, which are meant to give more information. And that was just published about the first week in September.

And we had some guiding questions which framed the work that we're going to talk to you

about today:

Which contextual forces shape our discussion of the utility of sequencing in newborns?

Under what circumstances should newborns be sequenced?

How should state-mandated newborn screening programs use sequencing?

What role should parents play in determining how sequencing information about their infant is used and stored?

And should sequencing be part of routine pediatric practice?

And I'm now going to turn the clicker over to Josephine Johnston, who's going to present remotely from the Hastings Center in New York. And I think they have a system here about how they're going to do that.

(Brief pause to set up audio)

DR. JOSEPHINE JOHNSTON: All right. So thanks very much, and thanks for allowing me to

present remotely. I realize that I'm not just a voice from the ceiling, but I probably sound like I'm from far away, because I was, indeed, born in New Zealand and have this accent that distinguishes me usually. So I hope everybody can follow along and understand what I'm saying.

So I'm going to present a little bit about the findings of our project. And broadly speaking, the findings -- I like to think of them in two categories: Analysis and recommendations. So will sort of make that distinction as I go along.

As Barbara and Cynthia said, this was a project that we at Hastings Center worked with Barbara and her colleagues at UCSF, under a subcontract from their NSIGHT project. And the Hastings Center, for those who don't know, is an independent research institute in New York.

Next slide.

So this is the cover of the special report that contains reflections and

recommendations, including the lead article, which is the analysis and recommendations from the whole group. So on the right-hand side, I've listed the authors of the lead article, which is what I'm going to talk about today. I'm not really going to talk about the 12 essays that we have in there that are really great, and I would encourage everybody to read them.

The Hastings Center Report is a peer-review journal; so everything went through peer review. And this particular issue report -- it's published by Wiley -- and it's available for free online -- so all of the 12 essays, plus the main lead article with recommendations and analysis are available for free. And the lead article was -- the lead authors were myself, John Lantos, Aaron Goldenberg, Flavia Chen, Erik Parens, and Barbara Koenig. And we worked very closely with all the members of the board, and those members are listed.

Okay. Next slide.

So yeah. I'm going to talk about the lead article, which is called "Sequencing Newborns: A call for Nuanced Use of Genomic Technologies." And I think that starts to indicate where we basically go with our recommendations. The first thing I want to discuss here is the analysis that we went through, because I think our analysis is as important, probably, as the recommendations themselves. This is a big terrain, and dividing it up and trying to sort of understand the factors that make decisions in one country different from in others was a big part of the work. So I want to spend a little bit of time on the analysis.

So next slide.

So the first part of the analysis is that we really thought about the fact that there are two broadly speaking -- two reasons one would use sequencing technology in newborns: diagnosis and screening. And it sounds obvious, perhaps, to

say that, but there can be a lot of slippage in discussion between these two reasons, which really are pretty different and play out very differently. So I think you'll see that in the recommendations, that the two purposes, or goals, do effect where we came down.

We also really kind of zeroed in, or divided up, the use of this technology into two types of sequencing. This is a little crude, but just to note that either the sequencing itself or the analysis can be targeted to specific regions of interest that would correspond, roughly speaking, to specific genes or variants that are associated with conditions.

Or it can be much broader -- on sort of whole-exome, whole-genome sequencing or whole-exome, whole-genome analysis -- which is much more of the sort of screening-type idea that you're looking for a lot of different things, or you're just kind of looking to see what you find. So, again, we thought that that distinction was

quite important, and I think you'll see that when we get to the public health recommendations in particular.

And then, broadly speaking, we divided the use of sequencing into three contexts, because very different laws or ethical kind of obligations apply in these different contexts, so we really felt it was important to distinguish.

Those three contexts here are: Clinical contexts, within which there's actually quite a big difference between the use in, say, sick newborns, who might be in the NICU, and then the sort of routine primary care clinical situation. So there's clinical context. That's one broad context where there are very longstanding sort of ethical principles apply to doctor-patient relationship, etcetera. There's a lot of analysis that happens in that clinical context.

Then public health, which is, of course, of major interest, I know, to the Committee. And then the US, of course, has the state-mandated

newborn screening program, In the other countries, it can be done at the national level.

And then direct-to-consumer. We really took seriously that direct-to-consumer was a piece that needed some attention.

The other thing I would just say before we move on is that we were looking again at the ELSI, which is really the ethical, legal, and social implications, of the possible use of sequencing for these different reasons -- different types of sequencing used for different reasons in different contexts.

And so, it turns out that different stakeholders are implicated in different ways -- you know, varying by context and purpose. And so we needed to do a kind of nuanced analysis, and that's why we used the word "nuanced" in the title, that these factors really make a difference.

And within that, the two, I guess, ethical principles or issues that most heavily

weighed on our board was the just distribution of benefits, and protections from harm. And we understood both those concerns quite broadly, so we were interested in a variety of different benefits that could come from the use of sequencing, including benefits sometimes to family members of sequencing newborns. And we were similarly broadly interested in different kinds of harm, including harms related to increases in expense, unnecessary follow-up kind of harms, uncertainty-related harms, and any harms that might occur to self-determination of birth child or the future adult.

Next slide.

So now, just getting to the recommendations. In the clinical context, we reviewed quite a bit of really positive and promising research on the use of targeted or whole-genome sequence for diagnosis in selected populations of newborns. So this is a lot of the work that Cynthia was talking about earlier that

Stephen Kingsmore's been doing, doing rapid diagnosis in the NICU.

And there were a variety of benefits that can come from that. It's not always the best-case scenario that the diagnosis is able to be made and a treatment initiated, but sometimes the benefits are slightly more varied than that, and they do not always result in changes in treatment, but they can guide meaningful care in other ways.

So there are significant benefits in that context. And it's also a context where parental permission can be obtained, where genetic counseling can be provided and follow-up care can also be initiated. So we felt that that was the sort of best-case scenario for the broadest use of the technology where there were the most likely to be resources available to really follow through on the various different kinds of result that they could return.

But we were not positive about the use of

sequencing as a screening tool in clinical context, and this would apply more to the routine pediatric care context, with limited usefulness in asymptomatic infants at this point. There were significant concerns over storage of results and possible discriminatory or insurance uses of the data that are just not resolved at this point enough for people to be offered this with assurances that it won't be used against their child, if you like.

And we thought there was really significant potential for results to generate unnecessary distress and to require counseling and to generate what is essentially unneeded or unnecessary follow-up care and monitoring, so could be very serious implications for the provision of care that are just not able to be addressed adequately right now.

So slide.

So just moving on to the public health context, which, of course, I know is of interest

to you. And Barbara and John are going to say more about each of these, actually, the public health context. But just to kind of go at the broad level of our recommendations, in the public health context, we were not persuaded that even targeted or whole-exome sequencing could be the sole screen for public health because it can't detect everything.

We took really serious, again, the concerns that parents and others might have over the storage of results, the storage of samples, and the possible discrimination or insurance uses following public health use of sequencing. And again, those same issues around distress.

So having said that, we were not looking right now to the kind of vision that Francis Collins has laid out. We were persuaded that sequencing could be really helpful if it was targeted as a secondary test following a positive screen, or as a primary screen to detect conditions that meet all screening criteria.

So I want to really emphasize that we took very seriously the criteria for inclusion of new conditions on newborn screening panels, and felt that if it were possible for sequencing technology to be targeted to conditions that meet those criteria, and concluding that states could afford to use sequencing as one of the ways to detect it, that it might be possible to use sequencing to expand what is currently detected to conditions that still meet the criteria but are not able to be adequately detected using other technologies or existing screens. So I'm sure we can say more about that in discussion.

And then, finally, next slide.

We looked at the direct-to-consumer context, and we were pretty conservative in this context, actually, so we did not think that direct-to-consumer use of sequencing technology for diagnosis or screening was a positive development. Parents, we thought, should not use this technology for diagnosis or screening. And

we asked healthcare professionals to recommend against the use of direct-to-consumer sequencing in infants and children to the families they treat. So we didn't see this as a positive development.

And then, final, next slide.

This is just the final slide showing the report again, encouraging you to access it online and to know that this was funded by all these different grants. So I'll take questions at any point.

DR. JOHN LANTOS: Good morning. Thanks so much for having us. This has been a great project for all of us, and it's fun to speak to the Committee and the audience about some of the things that we learned.

I sort of stumbled into this project. I've been doing bioethics for decades, but really had not gotten into the whole world of genomics. And Stephen Kingsmore was in Kansas City, and when this call for proposals came out, we looked

at it and saw that it had these components -- the sequencing, the clinical, and then the ELSI, ethical, legal, and social implications, component.

So we put together a grant, and luckily got funded. And so, as a result, I got to work with all these amazing genomics people, who I think are doing some incredible work, really, pushing the boundaries, and learned a lot, although over the course of the project, came to the view that geneticists are really a lot like teenage boys, and the bioethicists are like their mothers -- that is, they are out there, doing risky things that they think are a lot of fun, and we're saying like, no, no, no; be careful.

And so today I'm going sort of be a mother and talk about some worries, some concerns about work that seems really exciting, but first want to talk a little bit about why it's so exciting and some of the things that I really hope will come out of this.

Based on our project -- our project being Kansas City and now Rady Children's Hospital -- which was a project to look at whether doing rapid genome sequencing for sick babies in the NICU could lead to a diagnosis that would actually change the management of those babies for the better. And so the two big innovative aspects of this were doing genome sequencing on babies who hadn't had a diagnosis, and trying to do it quickly enough so that while the baby was still and unstable in the NICU, we could get the results back. Most people who do genomic sequencing take weeks or months before they return the results. So this took a whole lot of work, a whole lot of effort to try to both do the sequencing as well as do the interpretation and get it back.

The way we did it, first of all -- and this is crucially important, and I'll explain why towards the end of this talk. This study and similar studies were done in what I and other

people have called an "enriched population" -- that is, these were babies who were sick. They were in the NICU. They'd already had other testing, and the other testing hadn't revealed anything. So they were diagnostic dilemmas; they were mysteries. They were the most likely patient population to yield a result on a genomic test.

We also developed software to sequence only a limited panel of genes based on previously reported genotype/phenotype associations. So if a kid had seizures and hypoglycemia, we combed the literature for any gene associated with seizures and hypoglycemia, and then just tested those genes, which made it quicker to do the sequencing and much quicker to do the interpretation. So we weren't looking at the 3 billion base pairs; we were looking at 17 or 12 or 54 genes. And then the goal was to see whether (a) we would get results, and (b) whether those would influence diagnosis management or

allow a better prognostication.

Our hope for this was based on a lot of early reports of success doing this sort of thing, although when we looked at those reports, they were much more precise about what's been called analytic validity -- that is, the genomic sequencing was confirmed by Sanger sequencing; so the sequencing was accurate. And they were much more vague on clinical utility -- that is, whether getting these results actually made a difference for the babies who were tested.

And here are just some examples of some of the first reports of success; one came from our place. Just five babies, but in a similar population, we got a diagnosis in less than 50 hours -- that is, less than two days -- on four of the five affected babies. That gave us hope that this could be used. And this was back in 2012, just six years ago, but feels a bit like anxious history.

Around the same time, people were doing

similar studies in Columbia, and again, in these enriched populations, finding a pretty good hit rate of molecular diagnosis.

When people asked about usefulness, people said things like, "Oh, it led to discontinuation of additional testing." Well, duh. If you get a diagnosis, you don't need to do more tests. That seems like a curious claim. It was like, "We did a CBC, so we didn't have to do a white count." That's a benefit, I suppose.

Screening for additional manifestations -- always a good idea. Altered management -- I'll get to that in a minute. Novel therapy -- some familial testing. So if you get a genetic diagnosis testing, other family members is a good idea, and sometimes it leads people to change their reproductive plans, also a good thing.

People also talked about additional screening, appropriate social services, more accurate prognostic information, eligibility for clinical trials, and referral to specialist.

You'll notice here, there are not a lot of claims that it actually improved the clinical outcome for the baby who was tested. That's important.

But again, many people were doing this, claiming mostly 50 to 60 percent success rate in making a molecular diagnosis. Of note: When people did talk about the clinical usefulness, one of the most common changes in clinical management that occurred in these cases was discussion of a shift in the goals of care from life-prolonging treatment to palliative care. And that's going to be the first big concern that I raise, as a nagging mother, to bioethicists about how these tests are being used.

And what I want to do for the rest of the talk is go through two examples -- one, a specific clinical case, and then at the end, the case of screening for Krabbe, to show how ambiguity about the meaning of these tests might lead to clinical decisions that are, in fact, harmful.

So let's look at one case. This was a case from our place. We gave it a number in the report, CMH545. The baby was in the NICU and was having lots of problems -- had bilateral chylous effusions -- that's continued leakage of lymph into his lungs; remained on a ventilator for weeks and months, and eventually was nominated for inclusion in this study, got genome sequencing, and they found a gene -- there's the variant there -- that's been associated with a condition called Noonan syndrome. And the baby was given a diagnosis of Noonan syndrome.

This is, again, from the report. You probably can't see it, but there's CMH545. And those are the different clinical changes that could have happened. For him, palliative care was initiated. So he was diagnosed with this molecular diagnosis of a gene associated with Noonan syndrome on Day 69, and about two weeks later, after life support was withdrawn, he died. And this was reported as a case in which there

was a molecular diagnosis, change in clinical management, and the change was redirection to palliative care.

So what is Noonan syndrome? Noonan syndrome is a syndrome that's associated with characteristic facial changes. Most kids with Noonan have short stature. Some have congenital heart disease, and some have developmental delay, although most have normal cognitive and intellectual development; just about a quarter have developmental delay.

Doctors usually treat all the problems associated with Noonan syndrome. They get congenital heart disease, but these anomalies are usually treated the same way as in the general population. Developmental disabilities, if they have them, are addressed by early intervention and the usual things we do for babies who have developmental delays.

When you look at the genetics of Noonan syndrome, it turns out to be extraordinarily

complicated. There are many genes that have been associated with Noonan syndrome, but whether any of these genes are pathognomonic, whether they're diagnostic of Noonan syndrome is unclear. There have been no population studies of any of these genes, so we don't know how common they are in the general population. And these are just the most common ones. There's a bunch of other genes that have been reported to be similarly associated with Noonan syndrome.

So in this case, it seems there's a disease for which there are many genetic variants, each of which may or may not be diagnostic. The disease itself is not fatal, and is usually treated with efficacious interventions. The molecular diagnosis could be a false positive. And even if it's not, even if it's true, it doesn't justify the withdrawal of life support.

So in the report, it was listed as one of the clinical benefits of the molecular diagnosis.

So if that's true, it seems that was very bad clinical care. I work at Children's Mercy; we never do very bad clinical care. So I assume that was not really the reason why they withdrew life support, solely on the basis of a diagnosis of Noonan syndrome.

But if they didn't withdraw because of the Noonan syndrome, then what does it mean that they reported it as a molecular diagnosis with clinical actionability in reports that say 50 or 60 percent have a molecular diagnosis, and 38 percent of those led to clinical actionability?

My take-home lesson from presenting this case is whenever you read those reports, read them with deep skepticism, and look to see whether the claims of molecular diagnosis and clinical actionability are given with enough detail to determine if, in fact, either of the claims is reliable enough to hang your hat on. I think there's some -- dare I call it -- inflation of positive results in a lot of these reports.

And this is a pattern. There's few rigorous reports of the ways in which molecular diagnosis led to beneficial changes in treatment. And many of the reports of successful treatment are reported in the lay press rather than in peer-review journals, and usually, there's no follow-up report in a peer-review journal. So there's a fair amount of hype about these molecular diagnoses.

Our project was really meant to study it, and the project itself ran into some interesting problems. Here's how we tried to design the study: We wanted these babies who were in this population of very sick babies in the NICU to be randomized to either standard care -- whatever that meant; it was largely undefined and meant the clinical judgement of the neonatologist about what test to order -- versus standard care plus a whole genome.

And we wanted to see if adding the whole genome to standard care would lead to changes in

treatment, improvements in treatment, lower cost, shorter stay -- any recognizable clinical benefit.

We ran into problems even when we were designing the study, because even though the study had not been done, and even though whole-genome sequencing was new, nobody knew which babies might benefit. And the neonatologist said, "Well, if we have this test, we want it in all our babies. We don't randomize them." And we said, "The whole point is to figure out whether it works."

And so designing the study, we ran into two equipoise problems. One is, which babies are not sick enough to be worth the trouble. You know, if a baby has an isolated cleft lip or an isolated VSD, should you get a whole genome on them. The neonatologist said, "That's not going to help. We already know what to do with those babies."

Or babies who are too sick, who they

said, "We really need a diagnosis right away. We don't want them to be randomized to the standard care. We want results. We need them now."

So the eventual compromise for the study was any baby with a suspected genetic etiology. And that left room for clinical judgement. And we could only get the neonatologist to participate if they said, "But if he's really sick, we get to cross over. And if he's randomized to standard care and he's dying, we want to get the genome." And to get the buy-in of the neonatologists, that was the study design.

What we found, that over the course of the study, neonatologists became less and less willing to randomize their patients. Here are the results. The study started in 2014, ran through 2016. In 2014, they enrolled 64 patients, although of those 64, about half were randomized to standard care, and 12 of those, the neonatologist eventually requested that they cross over to get a genome as well.

The next year, they enrolled fewer, and there were fewer crossover requests. And the third year, they only enrolled 17. There were no crossover requests, so they were only enrolling patients who they were pretty sure didn't need a genome at all.

At that point, the numbers that were getting enrolled were too low for the study to reach its enrollment targets, and we started offering whole-genome sequencing outside the study, at which point, nobody enrolled anybody anymore. And you can see the clinical whole-genome sequence and targeted panel numbers of tests went up.

So neonatologists quickly lost equipoise even in the absence of convincing results. They just like this data, and like it a lot, and want it, and want it quickly.

So there was lack of equipoise at two different points: One at enrollment, and one once they enrolled at crossover. Doctors perceived

benefits without apparent harms, and this disequipoise makes rigorous evaluation difficult.

Let me just talk about one more example of the way that this can then be problematic, and that is if we take these results and take the neonatologist attitudes and incorporate them into a newborn screening program. An example that I'll use is one that I'm sure the Committee and many people in this room are familiar with. But I want to tie it back to what the implications would be if we're doing diagnostic testing here.

Many states have started population-based newborn screening for Krabbe disease, which is a pretty rare disease, but a devastating one. If kids have Krabbe, they have progressive neurologic deterioration and death, usually within the first year or two of life. The only possible treatment is a stem-cell transplant, and that's associated with many problems. It only works if it's done before babies are symptomatic, and so figuring out which babies are symptomatic

very early in life is the only hope for treatment.

So New York State started doing this. They used a very conservative approach to diagnosis. So first, they measured enzyme levels. If that was low, they tested for genes. If babies had low enzyme levels and a gene that had been classified as clearly pathogenic for Krabbe disease, then the babies were referred to a pediatric neurologist to see whether they had any early signs and symptoms of Krabbe disease.

The neurologist would do a detailed prenatal medical and family history, a comprehensive pediatric neurologic physical exam. They'd confirm the low enzyme level. They'd test the parents. And then they'd do a bunch of sophisticated neurologic tests -- MRIs, spinal taps, nerve conduction studies. So this was probably the most rigorous possible diagnostic approach, and an appropriate one, because after all, if kids were positive, you were going to

subject them to a potentially lethal stem-cell transplant.

What they found, in my mind, is really scary. So they tested 2 million kids. As expected, 99.9-plus percent were negative. Of the ones who were not negative, 620 had low enzyme levels. Half of those had one of the genes associated. And then, based on further testing, only about -- what would that be -- 5 percent of those were classified as high risk. So out of 2 million babies, 14 were though to have both the low enzyme level and the genes that are diagnostic of Krabbe disease.

But here's what was scary. They kept doing these neurologic exams to see how many developed symptoms, and they've now followed these kids for up to 10 years. And only 5 out of 14 -- that is only about a third -- developed any signs of Krabbe disease. Two-thirds of the people with what would be considered a gold-standard diagnostic test remain

asymptomatic.

Even worse, of the ones who were thought to have Krabbe disease, four went and got a stem-cell transplant. Two of them died within two or three months of complications of the transplant, and two survived with developmental delays just about as severe as you would have in Krabbe disease.

So Dimmock wrote a paper about this and said the state-mandated multimillion-dollar newborn screening program for early infantile Krabbe disease has failed to provide benefit. And there's potential harm both for receiving false-positive results -- the parents who were told, "Your kid's at risk for Krabbe disease," and nine years later, still hasn't developed it; but also for true-positive results, where you get a stem-cell transplant, and it either kills you sooner than you would have died otherwise, or leads to an outcome that's no better than you would have had with the disease.

How do these two tie together, my Noonan syndrome case and the Krabbe case? Imagine what parents might choose if their baby was in the NICU and had whole-genome sequencing that showed they had the gene for Krabbe disease, and they were on a ventilator. Most parents, many parents might say, "Oh, well, let's redirect care and choose palliative care" -- even though two-thirds of the babies with that genomic diagnosis, that molecular diagnosis, would likely remain asymptomatic for at least decades, if not their entire life.

We know now, because of the newborn state screening program, how bad what we thought was the best available testing is for Krabbe disease. For all the other genes on the panels that doctors are using in the NICU, we have no idea how bad they are, because we haven't tested 2 million kids and followed the ones with positive tests to see whether the tests are true positives or false positives.

So in conclusion, I think whole-genome sequence will be widely used based on these dramatic case reports of success in highly enriched populations. The more it's used, the more results it will generate. Some of those ambiguous results will likely lead to harm. And what we need, I think, to move this field forward -- because I think there is huge upside potential of using these tests widely -- is a little more rigorous science, and case reports that document cases in which there are harms as well as benefits, and honestly acknowledging that this is not all sweetness and light, but there's some darkness in this field as well. Thanks.

DR. BARBARA KOENIG: Thanks, John. That was really helpful.

So I'm going to just continue in this vein and tell you a bit more about some of the complex reasoning that went into our report.

So this idea of the promise -- and so it's not just Francis Collins who's been talking

about the promise here. This is a quote from Bill Clinton. And so continue thinking about this issue of the mommy bioethicist and the teenagers, because I think the teenagers are really pushing enthusiastically on things.

So it's a ubiquitous, I would say cultural trope, as an anthropologist -- this idea that it's going to be almost magic. I think it won't be too many years before parents will be able to go home from the hospital with their newborn babies with a genetic map in their hands that will tell them, "Here's what your child's future will be like." Okay.

So I think John has just given you a good example of why sometimes that's over-promise, and suggests, actually -- I think the main lesson here is that we're having a really hard time being patient. So, in a way, our report mostly recommends patience as a virtue. And that's hard when you have sick kids.

So the hope is that sequencing will yield

a correct diagnosis that hadn't been made already for a treatable disease, and treatment will lead to better outcomes. And we'll do this consistently and cost-effectively in broader and broader populations. So that's the hope.

I want to give you some preliminary conclusions from our UCSF study of the newborn blood spots from the California Biobank. And I'm going to say that these are some preliminary results that we presented at ASHG in 2017, because our project -- we tried to actually also listen to some of the technical issues.

And so our team, which actually looked -- we're now up to we've looked at about 1200 different examples of cases that were either false negatives or false positive from the California newborn blood spot collection. And we concluded that whole-exome sequencing -- and so we compared whole-exome sequencing with MSMS. Our conclusion was that whole-exome sequencing was not recommended as a standalone -- and "standalone"

is the key thing here -- tool for primary public health newborn screening for inborn errors of metabolism, and targeting the general population.

And so you can see in this slide -- the red box is why we think you need a sort of slow-down stop light. Missed cases and high false-positive rates render exome sequencing unsuitable for newborn screening or metabolic disorders in the general population.

And then, but the green light is that in several MSMS screen-positive cases, sequence data provided information that did help inform diagnosis, or might have.

So in summary, DNA may play a key role as a second-tier test. But what we found, it really depends on the disorder, the gene, or even the particular variant. There's just so much that remains unknown. So I think this issue of uncertainty and the need for patience is the main theme.

This is a slide that I got from Aaron

Goldenberg based on his work with Beth Tarini about the complex -- looking at this issue of how -- as you think about whether you're going to use sequencing, starting with the idea of sequencing single genes, an entire state newborn screening panel, whole exome, just looking at the protein-coding genes, or whole-genome sequencing -- how as you do sequencing in those different contexts, you get more and more complexity about the ethical, legal, and social implications. So, again, just a general point. I'm giving you the considerations that we thought about.

Other unique features of newborn screening of the public health use of sequencing. Well, we have to remember that these samples that we are looking at and this action is an unconsented practice. And probably, that's going to be a problem. The legal justifications for newborn screening are probably not going to hold if you move into using sequencing as a technology. Just the premises will not be there.

And I'll say a bit more about that as we move forward.

And although this varies from state to state, samples are stored in the California Biobank and available for research. So that's another unique feature of this. So the sequencing data would then be stored also.

Okay. So the public health context, sequencing would identify numerous conditions that do not meet the legal and ethical justification for state-mandated screening and for which states cannot provide follow-up care.

So we argued over and over again that the preservation of the screening programs is critical for public health and equality, so we wouldn't want to jeopardize those programs by an overaggressive assumption of sequencing as a tool.

However, we did believe that sequencing could be used as a secondary or adjunct tool for detecting conditions that meet traditional

newborn screening criteria. But you do need to have additional considerations regarding this issue of how you store the return of secondary results and storage of data. And I'll say a little bit more about both of those things.

Again, Aaron and Beth's work, Beth Tarini's work -- so when they actually talked to state newborn screening programs about what their concerns were about sequencing, this is the list of issues that came out of their work with the state:

That workforce and cost was a big issue.

Education and communication. The education -- we know from our clinical projects, as part of NSIGHT, that explaining sequencing to the parents is s very difficult task. So education and communication.

Incidental findings -- I'll say more about that. They're built in. Incidental findings are built into using sequencing.

There's also the impact of private

companies and the potential to drive to implementation that could become a burden on parents.

And then, again, I've already mentioned the impact on the original intent of public health newborn screening.

So our general conclusions in our project is that thus far, whole-exome sequencing has only been shown to be useful in clinical populations where diagnostic uncertainty is a barrier to good care. And even there, it's not yet totally a clinical practice, although I'm hearing more in more in my own institution that people are starting to say, "We need to sequence every child in the NICU." Now, that may, indeed, happen, but it's still going to take a long time before we fully understand that.

So I'm going to read this. So the other conclusion that we came to, there is not -- and I put "yet" with a question mark -- there is not yet evidence that sequencing every newborn would be sufficiently beneficial to children or

families to justify using it in a routine care, public health, or as a DTC service.

So we really struggled with this issue of is this just a lack of knowledge? And as knowledge accumulates, will we have an answer? And it's a bit more complicated than that. So we kept asking ourselves, are our recommendations -- were we the sort of conservative mommies here simply as a result of lack of data, and that these are time-bound recommendations? And will the accumulation of evidence solve the dilemmas of sequencing newborns? And the answer to that is sort of: Yes, but.

And I just want to take you through a few ideas of thinking through why this test is different from other tests, why the use of sequencing is different. And I'm going to talk about three categories. We've talked a lot about uncertainty. So those are the key things to keep in mind: The uncertainty of findings; interpretation requires broad data sharing, and

which really is transforming the nature of how we practice; and then the third area is the return of secondary or -- currently, mostly called "Unexpected findings."

So why is this test different? And I think I originally worked on this talk around Passover, which there was a theme of why is this day different than other days. So the idea was data are everywhere. You get so much data from sequencing. And then you need to interpret it. You have, then, the problem: What should be returned? What is actionable? Dr. Lantos just talked about that in great detail. And then we also have the ubiquitous issue of managing variants of uncertain significance.

And I have the privilege at UCSF -- I sit in our exome sign-out rounds when we do interpret. And for each case that we do, we get, you know, several hundred variants that have to be carefully thought through. And that's what happens in the clinical context. And the same

kind of data might be generated in a public health context.

All of us in this room have lived through the issue of thinking through how we should return secondary findings. This is just a slide to remind you that the ACMG now has 59 recommended conditions. In our projects, it was a consideration that we made in terms of what we would actually return to families and think about them.

The other way in which this test is different is that it inevitably affects families, because you get these other issues that might reveal that there are other carriers in the family, other cases in the family for reproductive planning, everything else. And think about it this way, in terms of something like -- this is just a slide of a classic BRCA1 pedigree, so that you see an adult-onset condition -- a dominant adult-onset condition.

So think this as an ethical dilemma. You

have a newborn -- or maybe one of the ones that Dr. Lantos just described -- a newborn in the NICU with undiagnosed anomalies is sequenced. A known pathogenic variant in something like BRCA1 is identified, and Sanger confirmation reveals maternal inheritance. So what should the team do? And does it matter if it's the research context or the clinical context? And how are those getting a bit mixed up here? So some people would argue, well, just don't interrogate that part of the sequence data. But it's going to be there, so that presents some challenges.

So what do you do when you identify a child with an adult-onset condition? So historically, in pediatrics, we've been pretty clear about that, that we don't return those conditions to children because of a fundamental commitment to respecting the autonomy of the child and the child's right to an open future, and also to protect the child from the potential psychosocial harms of having these kinds of

expectations, part of the way their parents think about them, etcetera, into the future.

So those are the arguments against returning. And I thank Ingrid Holm, who's one of the leaders of the project in Boston, for helping to think this through. They actually had a case exactly like this which they had to deal with. But in their case, they actually decided in favor of return, because they tried to look at this in a new way, and think about the obligation of benefit to the affected relative -- in this case, the mother. And also, professional integrity: just the idea that if you know something about this family, about this mother, and she doesn't know it and has no other way of knowing it, then your obligation to provide benefit as a clinician trumps these other considerations for the child.

And finally, the health and life of a parent. Even if you're thinking about best-interest standards, the health and life of a parent is clearly in a child's best interest to

not have a mother who dies early of a disease that might have been presented. So this secondary findings issue is just ubiquitous in sequencing.

So I ask you, what if this same variant were identified in the context of state-mandated or expanded newborn screening? Creates even more complexities.

So, again, why is this test different? Well, it's different because we don't yet have the large and robust databases to interrogate all the variants and to understand them, and there's so much variability. So variants can only be understood when compared with the referenced databases, which can only work if data are broadly shared. And we have many barriers to data sharing. We also have uncertainty in interpretation, particularly for ancestral-diverse populations. I'll say a bit more about that in a minute.

And we also have this phenomenon going on

now of the transformation and the demarcation between research versus clinical care, or a standard public health practice -- between research and standard public health practice, because we are increasingly needing to maintain these databases that we collect in clinical care and constantly be looking at them over time and reanalyzing them. So this is very costly and very complicated.

On the issue of whose data are in the databases, this is a slide from Nature a couple years ago by my colleagues Alice Popejoy and Malia Fullerton, which shows that we -- the other problem that we have is we have a systematic bias in the databases that are available in that -- and they just look at the actual data in 2009, comparing in 2016, of what percent of the databases that are used for interpretation are from individuals of European ancestry.

And you see that it's gotten a little better; it goes from 96 to 81 percent. But even

so, we still are much more likely to get variants of uncertain significance in certain populations. And that's an ethics issue; that's an issue of health equity -- you know, how do we change that.

And this also suggests a critical need for robust community engagement as we're thinking about all of these issues -- having to do with making use of sequencing.

I also want to just point out one other social justice issue that is at issue, and that is the issue of insurance coverage for things like sequencing. And that applies across the use of sequencing in clinical context as well. And this is just the cover -- an article from a recent Genetics in Medicine paper by a colleague of mine at UCSF: "Private payer coverage policies for exome sequencing in pediatric patients: Trends over time." And it was the first in-depth review of private payer coverage in pediatrics just with neurodevelopmental disorders. And I'm not going to give you the

details, but just the bottom line is there's very little coverage that -- the insurance companies are just waking up to this, and they're only now understanding it. But this is an issue of health equity, too, in terms of who has access.

So further considerations: Will identification of rare disorders not currently screened for by state newborn screening programs advance our understanding of conditions currently not recommended on the RUSP? Well, those issues were discussed in detail in many of the sidebarred issues in our report. And this is a difficult question, but of course, the answer is yes, but it's how much patience do we need before we actually implement this, and how can we do this in a way that protects the interests of children.

And finally, Diane Paul, who is a very distinguished historian -- one of her sidebars deal with a really important additional consideration, which she calls a little bit of a eugenics redux: What are the implications of

adding reproductive benefit as a rationale for newborn screening? And those implications are not trivial. This moves well beyond the best interest of the child, which has traditionally been what we've thought about. And will this be considered some kind of state-sanctioned eugenics? And I think it's important that we keep that on the table.

So we can come back to our -- I'll maybe leave up during our discussion our guiding questions. And thanks very much. And we appreciate the opportunity to present our report.

DR. JOSEPH BOCCHINI: I want to thank the four presenters for really excellent presentations. I think you've given the Committee really the state-of-the-art and the current potential benefits and harms and variety of different utilizations of next-generation sequencing. So I think that's been really helpful to the Committee.

So, Operator, if you'll open the lines of

our organizational representatives, and let's open this up for discussion, comments, or questions, first from the Committee.

DR. MEI BAKER: Thank you so much for this very comprehensive panel presentation. I just want to share some of myself, the reflections to listen to that. First of all, the funding -- the challenging you present here -- I want to say is not a surprise. The couple reflection I want to share is: Why do we talk of newborn screening and compare with NICU babies, sick babies. The idea, the purpose that you think is very different.

So recently, I was at another conference. Something be said, I think, is really articulate very well as in my mind for a long time. So when you're dealing with the whole population, newborn screening, the purpose is you provide the parents assurance their baby are fine. But when you're sick babies, your purpose is to find cause. So that's very different. So I think it's really

important. I think that people in audience understand why I said that. I don't to elaborate more.

The other thing I want to say is that during the presentation, when you say "Sequencing," I know you are referring to whole-genome sequencing. But I would suggest maybe start to use the term whole-exome sequencing. The reason I said that, gene sequencing is a technology. It's being used in newborn screening right now. But the fashion usually way is a gene target -- target a gene, target a mutation, target variants. This is a very different flavor. So I'm still worry about people get confused.

So I give you example, like CF. People using next-gen sequencing to do the second-tier, CFTR mutation for this. So I think you need to be careful because the principle utilize technology because next-gen sequencing, right now, it's only the mean. You can simultaneously

detect a large disease-causing mutation. People utilize that.

And another way I want to introduce this is you imagine in terms of tiers, when, what to do. And also, I feel that data analysis can be staged. I go back to the CF, because we have our experience we're using right now, because we don't want to have the mutation identified you do not know the consequence. So the panel -- we have large panel, 270 -- utilizes CFTR -- two database. So this is the large -- the easiest cause of mutation. But when we have one mutation identified, we still don't feel comfortable to potentially have disease, so we still recommended the sweat test. But when you sweat test, anything's beyond 30, we reanalyze the data, because the raw data is a whole-genome sequence, the data there. Because this practice actually allowed us to find the new mutation, the disease mutation. I think things evolved, so we still have so much to learn. So this is one part I

want to say.

Second part is, I think we need be careful conclude gene sequencing shouldn't be the second tier. But you do have this -- just come and saying depends on disease, depends on -- I think it -- I would emphasize the second part first, before say second tier, because it really is a disease-dependent.

Certain disease make perfect sense that use a -- metabolize as first tier. I go back at CF again. CFRT is not good marker. We have a false negative -- quite a bit of false negative. Because of the time, I don't want to get details. If we have the way, have the principle for the process to do it with a carrier, I would think it's not totally unreasonable think about the screening for CF, use gene test as a first tier. So I think we need be -- just be careful to think about that.

DR. JOSEPH BOCCHINI: Any comments from the panel?

DR. JOHN LANTOS: Just briefly. I mean, I think the more narrow the target of sequencing and the more it's used in conjunction with other tests, the better it will be. So I agree.

DR. BARBARA KOENIG: I just also would point out that there's a quite clarifying essay in our special report by Robert Currier from the California Newborn Screening Program, describing in great detail how the targeted analysis of CFTR is done in our program, which is very helpful and lays out exactly what you just said. Yeah.

DR. JOSEPH BOCCHINI: So I just want to remind everyone, before you answer or speak, please state your name, so we have it for the record for the transcript.

So next I have Beth, and then Melissa. Okay.

DR. MELISSA PARISI: Melissa Parisi. So I will take a little bit of umbrage with the comparison of geneticists to teenage boys because I think my preteen son would definitely not

characterize his middle-aged geneticist mother as a preteen boy or a teenage boy.

So first of all, I want to thank the panelists, because I think you all did an excellent job of really laying out a lot of the issues with regard to ELSI implications for whole-exome and whole-genome sequencing in the newborn period. And in fact, the whole purpose and the reason why NIH supported the NSIGHT program and these four awards was really to explore these issues in a thoughtful and systematic way. And I think each of the four programs has been different in its approach, and each has brought important considerations and enlightenment to the community broadly. So we're very grateful to you for presenting this and for putting this Hastings Center report.

I had two comments that I would like to make, and one sort of is a question, and one is a comment. First of all, John, in particular, when you were talking about the case of the Noonan

syndrome. And I struggle with whether or not you can classify the molecular diagnosis as having clinical utility in that context because I think that that was a very sick infant with Noonan syndrome, which is the exception rather than the rule. And probably the whole care team was trending towards palliative care, but having a molecular diagnosis sort of at least brought closure, whether or not that actually contributed in a meaningful way to the decision to the go to palliative care.

So, you know, I think that there are nuances to this. And what it really speaks to is the messiness of clinical medicine and the challenges that we have in terms of trying to come up with some general rules of play, particularly when things are not always clear-cut.

I think another example of this is really the loss of clinical equipoise in wanting to do the randomized trial in the NICU, because all of

the neonatologists were like, "Well, if there's a chance we're going to get an answer with this whole-genome approach, why wouldn't we want that?" And you know, again, in the ideal, perfect world, we would be able to complete our RCTs, and we would have full enrollment, and everything would be, you know, crystal clear and enlightening. And that's just not the messiness of our real world. So that's just more of a comment than anything. But I certainly appreciate your raising those issues.

With regard to the summary of the Ethics and Policy Advisory Board recommendations, one is sort of a call for a consideration of a little bit of a flexibility with regard to the public health context and the recommendation of potentially using targeted sequencing as a secondary test. Or we just heard about an example where it might be considered as a primary test in CF and other examples.

But I also think that there may be a role

for secondary whole-exome or whole-genome sequencing in the newborn context when you do have a positive tandem mass result, and potentially confirmatory testing hasn't really revealed -- a targeted testing may not have revealed the genetic etiology.

And I think the UCSF program in particular and some of the others have had examples where the whole-exome sequencing actually led to identification of a new gene associated with hyperphenylalaninemia, for example. And so I think in the research context, which, of course, I think is really critical, there may be a role for whole-exome or whole-genome sequencing as a second-tier test for those situations where we're not actually able to nail down the etiology. So that would be one consideration that I would have.

And then my second point, which is really kind of a question for the ethics community, which is the recommendation in the clinical that

results unrelated to diagnosis of the infant may be returned to families if those results could benefit family members -- so the whole issue of secondary findings and how to relay that information.

What I think we really need -- and of course, the entire ethics community in the genomic space is struggling with this -- what are the situations in which you decide what should be returned to families? I mean, we're obviously all using, or many clinicians are using the ACMG 59 genes. But I think when you're talking about a newborn, there may be different considerations for what's relevant not only to that newborn, but also to the family members.

And I also think it needs to be dynamic and flexible and change over the age of the individual. So this really speaks to what we call the dynamic interpretation of the genome over the lifespan of the individual, which is where I hope we are going as a genomics community

in terms of thinking about how to take these data and really make them maximal useful.

DR. JOSEPH BOCCHINI: Thank you.

Comments?

DR. BARBARA KOENIG: I just want to ask Melissa, do you think that when you do proceed to targeted sequencing, when you have a diagnosis, that you -- or when you can't explain a finding that we should go back to the family and tell them what's happening, or just proceed immediately to using sequencing as an additional test?

DR. MELISSA PARISI: I mean, I think right now, where we are in 2018, it should still be an informed consent-type decision-making process. But I mean, I don't know. I mean, I think the future -- you know, we don't know how to predict the future, but there may be some situations in which there could be a reflexive third tier genomic analysis that might actually shed some insights into the condition for that

child.

DR. BARBARA KOENIG: I just have one other quick response to your very helpful comments, and that is that I think -- and John and I have talked about this a lot over the few months -- but I don't want to leave the impression that referral to palliative care is a bad thing. You know, failure to delay the referral to palliative care care at the right time is actually a bad thing if you don't refer. So figuring out the right time is always hard. And if genetics can help with that, that could be, in some instances, a good thing. It's just very difficult to make that distinction.

DR. JOHN LANTOS: And I would like to just endorse and repeat exactly what you said about the Noonan case. It's unlikely that the genetic molecular diagnosis was the sole reason they redirected care to palliative care. In fact, I've discussed this with both the genomics folks and the neonatologist at our place, and

they said, "Oh, no. That kid was so sick. I mean, we were going to do it anyway."

But two things. One is: What is the role of imperfect genomic knowledge in giving the final nudge? I think that is important to study. And the other is: What is the rationale for then reporting that this was a case in which a molecular diagnosis led to a change in clinical management? That seems a bit exuberant and perhaps even misleading.

DR. MELISSA PARISI: Yeah. And I agree with you, John. But I also think that there's something to be said for having an explanation for that child's extreme situation. In some ways, I don't know if it -- "giving permission" is not the right term to use, but it sort of allows people to say, okay, we've got a sense of closure. We don't need to keep looking for something that might have a treatment that's going to allow us to turn the course for this very sick infant.

DR. BETH TARINI: So I'm glad I let you go first because you clarified my question, which was initially about this diagnostic test issue that Dr. Lantos brought up, which was, well, it's just a -- what I heard was the neonatologist saying, "It's just a test." And this, I think, very important distinction between a diagnostic test is that provides you something that gives you closure and/or therapy that helps you, and something that may insight a change or behavior and action that could harm you.

So almost like this someone innocuous view of testing, because I think it correlates very well with what you said, Melissa -- that is, like it's messy. Medicine is messy. We all know it's messy. It's even messier when the child is on a ventilator, is on pressers, etcetera, etcetera. And if we give in to this -- there's a nuance here -- if we give into it's messy, without striving to de-messify it, if you will, then we, I think, get into a slippery slope of

it's complex. Like often, in my short administrative career, people have told me, "It's complex." And then there's no further discussion about what is the complexity or disentangling it. And that's not helpful; in some cases, it's obfuscation -- intentional, not --

But in this case, when we fall back as providers, messy, it invites us potentially of a slippery slope of, well, it's messy. It's hard to tease apart. The child's dying; I need to act. There's an intensity. I'm just doing a diagnostic test.

And the neonatologists know this very well, because oxygen -- we breathe oxygen, right? And it seems like an innocuous substance, until you give a little bit too much, and the child loses their sight, or you give not enough and it -- so yeah. But oxygen is an intervention. So then you fall back into this issue of like, well, that's an intervention and a diagnostic test; it's not an intervention.

However, it seems here that a diagnostic test, in the example of Krabbe, is now emergency as a potential intervention because it is giving you information that potentially could provide, in a hypothetical, an action that may be potentially not fully informed. And so I'm significantly concerned about this lack of randomizing these children, because we've created this situation where there is no harm to the diagnostic test because we never looked for it. But it's messy, so we can't look for it. And it's urgent, and they're dying, so we don't have the time to look for it.

And I'm concerned that what happens is -- as my husband always says -- we've not actually solved the problem. The problem continues to exist. It will just re-emerge in five years when we get a case report of like, well, how did this happen, and why did we not tangle with all these issues sooner?

So my summary point is, one, messy is a

tricky frame because it -- we cannot allow it to get us into this piece of acceptance, this slumber of acceptance. And two, now this raises concerns for me of -- from an IOB and ethics perspective -- should a diagnostic test now -- like sequencing -- be given the same sort of assessment as one would do a therapy in the hospital -- or you know, a therapy when an IOB intervention's considered.

So my question, then, on the second, is to Dr. Lantos of where, from an IOB sort of trial perspective, does this leave us?

DR. JOHN LANTOS: So two quick responses. One, there is a bit of genetic exceptionalism here in that we don't usually subject diagnostic tests in the NICU to randomized controlled trials to figure out whether to use them. I mean, neonatologists decide whether to order micro arrays or MRIs on discharge or anything else based on their clinical judgement. So the idea of demanding a randomized trial is already put in

genetic testing, holding it to a higher standard than others. There, I think, maybe reasons why that's justifiable, and that's part of what our whole project was about.

Second point, yes, it's messy. And the question of when a genomic result should lead to a change in management, either a stem-cell transplant or a redirection of care to palliative care is sort of where the action is ethically. And pointing out cases where it is used appropriately or inappropriately will further that agenda in the right way. But just saying, oh, you know, it may not have been appropriate, but -- and I'm not saying you're saying this -- but you know, oh, we got the diagnosis of Noonan syndrome; it gave closure -- except a diagnosis of Noonan syndrome should not give closure about a decision to redirect to palliative care. The kid was sick enough that it was a good reason to redirect care. You shouldn't need the diagnosis, and the diagnosis shouldn't buttress the

decision.

DR. CARLA CUTHBERT: Carla Cuthbert, CDC. This is just a quick comment. We really appreciate your presentation today. And I just wanted to let you know, I think some of you may have known that I got my entire branch to review all 12 of your essays. And we had that as a three-hour learning opportunity. So that was really good, especially from the point of view of laboratorians to be able to focus on the ethics associated with our testing.

It was specifically well received by our Mass Spec folks, who looked at next-gen sequencing and said, "I don't understand this." But they really did benefit, so I really do appreciate what you've actually done.

And again, I would just like to reinforce some of the ideas that you mentioned. But yes, I don't believe there's anytime, I think, in my future that next-gen sequencing will be a first-tier test where we're going to be doing

that in its entirety. There are just too many unknowns. We're finding with some of our programs already that are doing sequencing, and we're working closely with them, just the variants of unknown significance, those are hard to characterize. And we know that as we're looking at those, it's going to be a long-term effort to have to go back and try to understand what these actually mean in the context of these children as they grow.

And again, with respect to APHL's Molecular Subcommittee, these are questions that those who are actively engaged in molecular testing have had lots of conversation' about. And they have identified some need for being able -- especially the states, as they work individually, to do their own kinds of sequencing, to be able to have a place where they can pool some of their information and their data, and to have tools that would be helpful for them as they are looking at the data that they

collect.

And also having an opportunity to make that data available to the public so that that actually gets pushed forward on a very regular basis. So these are things that they are actively involved in discussing, and I know that, you know, as time goes on, we'll have more and more opportunity to have them describe just some of the things that we're actually involved in. But I just wanted to say we are really appreciative of your comments today. So thank you.

DR. JOSEPH BOCCHINI: Mike. Please state names.

DR. MICHAEL WATSON: Yeah. Mike Watson. Now I remember why I don't bring my mother to work with me. So I acknowledge most everything you said is -- you know, Krabbe is a unique example, and there's lots of problems. I think most newborn screening programs acknowledge the issues there.

But I think the problem is not so much be patient and go slow, because this world ain't going slow. I think it's actually the system in which we do clinical investigation. You know, there was always this place between research and standard of care where lots of clinical investigation happens, and it seems to have fallen apart. You know, we used to have really well-controlled national cooperative study groups in cancer that raised the bar on almost all practices that were done by people involved in studies.

We have coverage with evidence development now that, you know, if you want to do something that is translational, then you better provide evidence, or we're not going to pay you for the work you did. So I actually think there's other solutions to the problem rather than going slow.

DR. ROBERT OSTRANDER: Bob Ostrander, American Academy of Family Physicians. You are

supposed to be advisers to the Secretary about these genetic newborn issues. And the thing that struck me most about this talk -- which, by the way, was terrific. And I'm going to try to get the American Academy -- make this rise to one of the areas they look at.

But one of the things that struck me the most listening to your talk was this whole direct-to-consumer piece. And you did mention that. I mean, if we've got ethical issues in the NICU with this, if we have ethical issues in the state newborn screening programs, we really have ethical issues allowing companies to market this stuff directly to people without letting them know about all these horrible, potential harms. And I wonder if the Advisory Committee might advise the Secretary to consider promulgating some regulation of that industry.

DR. JOSEPH BOCCHINI: Josie, are you still on? You want to take that?

DR. JOSEPHINE JOHNSTON: I am still on.

And I wanted to comment on a few things. But I thank you for that comment about DTC. I'm not sure about regulation as opposed to other ways of intervening, but I do think that there's a long way to go to helping consumers be steady about the kinds of products that are being marketed to them in the space. And by "in the space," I mean genetics and genomic gene, not really just around newborns. So I definitely think some action needs to be taken -- significant action to help make it possible for consumers to make informed choices about what they're actually purchasing and what it can really tell them, and list some of the risks and downsides associated with it.

I also wanted to say, in response to the person -- I'm sorry. I'm not able to completely keep track of who's been saying what. But around the "it's complicated" issue, I don't know that there's agreement, exactly, but it was very important for us to introduce a sense of nuance into this discussion, in part because of some of

the very broad-sweeping claims that are being made about the usefulness of sequencing and its inevitable ubiquity, including in children.

So we weren't exactly trying to say "it's complicated," and we certainly didn't throw up our hands. But we really wanted to introduce some nuance so that uses of the technology can be clever. And I think, in that way, we're actually combatting a kind of genetic exceptionalism, which would say that, of all the different medical technologies around, sequencing's the one that everybody should use to its fullest extent, which is, you know, a kind of exceptionalism because there isn't really much in the way of medical technologies that one would say that about. Thank you.

DR. BARBARA KOENIG: This is Barbara Koenig again. I just would like to respond again. I think there are a couple things on the table. I agree with Mike Watson, that we are at an inflection point about some fundamental

changes and how we come to understand what we know to be right and true in research. And those are very complicated and difficult, but we do need to keep teasing them apart. And it's especially problematic with sequencing because of the issue of the role of the FDA, etcetera, etcetera, all those kinds of things.

But I want to come back to the question that we kept asking ourselves: Is this just a matter of accumulation of data and that we'll eventually get it right; it's just like a computational problem? And I'm working with some computational biologists at Berkeley in our next project, building on NSIGHT project. We've just been funded by the Chan Zuckerberg initiative to really look at more -- you know, to develop these machine-learning and AI-informed approaches to interrogating the genome, which is -- because of the volume, that's the only way this is going to move forward. So that's where the research is going, and that will undoubtedly have some

progress.

But that is up against the fundamental issue there's so much we don't know about the nature of the human genome and how it reacts in particular environments, and how predictive, actually, will it be. And those are things that are, you know, philosophical as well as -- so that's why we kept trying to keep some of this complexity on the table.

DR. JOSEPH BOCCHINI: We have Dr. McCandless and then Kellie and then Beth.

DR. SHAWN MCCANDLESS: Thank you. The topics you brought -- everything you said was excellent. I do think, as a geneticist, though, I want to reinforce what Dr. Lantos said a few minutes ago, which is that we really need -- and this Committee needs to be very careful to avoid the concept of genetic exceptionalism as we think about genetic testing particularly.

Yes, these are complex tests. Yes, we don't understand all the utility. But at the end

of the day, DNA testing is a type of medical test that provides information. It doesn't give us the answer. DNA is not entirely deterministic. But it does help us to understand what's going on with people. It should be viewed in that way. It should be viewed as any other genetic test. We should not hold DNA testing to higher standards than we hold other things.

And in particular, I think there's an important point about how we interrogate the literature about genetic testing. I think we're holding genetic testing to a much higher testing than we hold many other types of tests, or basically anything in medicine. And I would refer you to look at the surgical literature, if you really want to look for examples of how we, in the field of genetics, are above and beyond in terms of the quality of the data and the nuance that the recommendations are made with.

I would also point out -- and I acknowledge Cate Vockley for pointing this out

too -- that when you see clinical utility or actionability in a publication, that is a direct response to who we pay for healthcare in the United States. And we can't get genetic testing paid for unless there is documentation in the literature of clinical utility and actionability. And so we are required -- to ever move the field forward and to ever move clinical care forward, we have to publish things that say that. And so we can thank our colleagues in the insurance industry for that perhaps oversimplification of genetic data.

The second point that I would like to make is really on behalf of the Society for Inherited Metabolic Disorders. And that is that newborn screening for these rare inborn errors of metabolism has rocked our world. This has changed how we practice medicine.

And I just want to encourage, on behalf of our organization and behalf of our patients, I want to encourage you all to keep your eye on the

prize of newborn screening. It's a screening test to identify children that we will be able to intervene and make a meaningful impact in their life by early diagnosis.

And if we get too far into the weeds with whole-exome sequencing and all the complexities that are involved in that before the time is right, we really run the risk -- and I'm not the first person to bring this up in this meeting -- but we really run the risk of throwing out the baby with the bathwater. And I really just want us to keep our eye focused -- keep focused on what we really need to do, which is to strengthen and enhance the newborn screening program in the United States. Thank you.

DR. KELLIE B. KELM: Kellie Kelm, FDA. I just wanted to clarify that the products -- for example, direct-to-consumer medical tests that the FDA actively regulates, that were involved in -- 23andMe is actually only authorized for 18 and up. And they actually ask people, when they send

in their product, "Is this for someone who is 18?"

And so that is basically them doing their due diligence. It would be hard to ask them to do anything more than that, but it is something that we consider as we work on products: What is the population that's appropriate and ethical standing for that, if you will. But you know, I can't speak to other products where a prescription, laboratory-developed test pathway might be there. So --

DR. JOSEPH BOCCHINI: Thank you.

I've got Beth, Debbie, and then Carla.

DR. BETH TARINI: This is Beth Tarini. I appreciate Dr. McCandless's comments because they're very important in clarifying that we cannot hold -- I do think you're right to say, "Oh, we can't give genetic exceptionalism that we don't give other tests." And I'm sitting here, thinking, like, what's the definition of a diagnostic test, you know? Like does it mean --

you know, is it a certainty issue? Is it a confirmatory issue?

But the other issue is -- the challenge is not conflating the ethics of the study with the efficacy argument and the cost. So we can argue, it's not exceptionalist. Don't require to go through an RCT. Don't require this what you wouldn't require an oxygen probe, right? That you don't require this for an MRI, right?

But on the same -- that's fine, but then someone's going to have to pay for it. So then, on the backend, the payers are going to ask you: what's the efficacy? But you don't have the efficacy because you didn't do the study. Or you did a study, and you didn't do it in a randomized way; you did it on a quasi-experimental way -- it has limitations. And that's fine. Again, the challenge of what is the incremental benefit that the payers will then ask you for. And we could have a whole separate discussion on whether they care or not. But that is the question that will

be asked. And what is their motivation? We get a whole separate conversation and seminar.

But they will ask you: What is the benefit of this technology intervention/testing? And you will be asked to provide it. We all know this because the geneticists here try to get their genetic tests, right, funded, and spend much of their time doing it.

And in order to answer that question, we must have data. And when we publish clinical utility, it has to be based on, I would think, studies and data that not are just published, but are based on actual studies that, with respectable limitations, can actually demonstrate it. So that is not exceptionalism. That is health services in the United States, and how to finance them. And so that genetics still must defend itself within.

DR. DEBRA FREEDENBERG: So I agree with both Melissa's and Shawn's comments. But there are a couple of other things that I think we

really should start thinking about too. One is that right now, there is a disparity in the ability to get genomic sequencing. Most geneticists, and even a pediatrician, if they tried, spend hours and hours trying to get authorizations, and get repeated denials, and lots and lots of time.

So the perception that this is out there in random usage, I think, is not correct. And it may be just a fiscal restraint, but it doesn't happen daily and routinely and without thinking. And I know that many people have commented on your Noonan's, and my question is: Where was the clinician? There should have been a clinical diagnosis on that child where, you know, maybe you didn't really need the molecular diagnosis there. But that's a whole other story.

The second comment, also, is that as we talk and consider sequencing, it's going to involve fundamental changes to newborn screening programs. We, in my state, do do some

confirmatory testing and do do some sequencing. And I can tell you, there are hours and hours of conversations, about what the responsibility and the duties of a newborn screening program is. And I think that's something we all should consider in terms of do you have to have a variant of unknown significance? Whose responsibility is it? And how often do you have to reanalyze your data? And who's going to recontact the family or the healthcare provider?

So there's kind of going to be a fundamental shift in the way a newborn screening program operates, and we've seen that beginning over a longer term than just in our short-term -- what we call short-term follow-up. And there's been discussion about changing, quote, "Short-term follow-up."

But I think we really need to think -- if we're thinking specifically about newborn screening programs -- how this is all going to impact the programs and where the fundamental

changes are going to be within the programs.

DR. JOSEPH BOCCHINI: I think I have to give Carla the last -- because it's already 11:30. So I apologize. I have to cut off the comments.

This has been an excellent series of presentations, great discussions, and I think we've all learned a great deal about where we are, and with adding next-generation testing for our babies.

So I want to thank all the panelists for their presentation. And now we'll move to the next session. So thank you very much.

(Applause)

We're going to stick to the theme of ethical, legal, and social implications -- turn our direction now to pilot studies and newborn screening. Dr. Jeff Brosco, Committee member and Chair of the Follow-Up and Treatment Workgroup will provide an overview of a recent publication on these considerations for newborn screening

pilot studies.

So Jeff.

DR. JEFFREY P. BROSCO: Great. Thank you very much, Dr. Bocchini.

It's great to be able to tell -- and I'll try to go quickly because I'm the only thing that's standing between me and my lunch. And I usually eat it around 11:00 a.m., so hopefully, I won't keel over.

So, actually, this talk fits in perfectly with a lot of the ethics issues we just raised, because Aaron Goldenberg and Michele Puryear, and a whole group of us said, well, we really need to have more data on these kinds of ethical questions. And so I'm going to tell you about the work we've been doing over the last couple years that just was published.

No disclosures. And these are my opinions, and not necessarily those of the Secretary's Committee.

All right. So just quick, to put things

back in perspective, right? When screening started in the 1960s -- and I have here a few pictures. You've got President Kennedy there with scientists that helped figure out PKU. You have, obviously, the Special Olympics picture there, talking about how important intellectual ability was in the 1960s and how critical it was to national policy. And just that's the new year which newborn screening started.

But what we don't know in the story and don't hear a lot about is that there were ELSI questions raised from the very beginning. And initially, when we were trying to figure out, well, how should we do this newborn screening, false negatives was the big issue. There was concerns that hospitals weren't screening, that we were missing kids. And that's actually one of the main reasons why newborn screening moved away as being a bedside test or hospital test to a public health mandate, was to avoid those sorts of issues.

Interestingly, there were virtually no concerns about parental consent. That just wasn't, really, in the 1960s, and important part of clinical medicine in general. And also, there were virtually no concerns about genetics, even though we knew at the time that PKU was clearly a genetic disease, and there were lots of genetic issues in the time. It really wasn't until the 1970s that the whole genetic exceptionalism idea really took hold.

More relevant to our issues today are what happened just five years later. So after the first million babies in the United States were screened, there was a large conference here in Washington, DC, not unlike this one. And it turned out there were a whole series of ELSI issues, which we will all recognize. All these indeterminate values -- what do we do with the in-between values? Who do we treat? How do we treat? What's the right level of phenylalanine in the blood? Are we treating too much or too

little? When do we stop? Is this a lifetime of treatment? Or can we just go for 5 or 10 years, until their brain's fully developed?

There were many false positives -- important to point out few physical harms. But there were concerns about what that meant for families. And there was this idea of iatrogenesis -- sort of the first publication talking about the anxiety that's built into test results coming out. So these issues have been around at least from the very beginning, as soon as we started newborn screening.

So the background is that based on our experience over the last 50 years, and even the last 5 years, we know that there are going to be ELSI issues that come up with every condition that comes to this panel to be added to the RUSP Board of State Panels. And I just listed here a few of the different things. I'm not going to go through them because you know them already, and again, lunch is imminent. But there are,

obviously, plenty of ethics issues that we could be facing in any particular condition.

So our premise was, as a group, that decisions about whether some -- a candidate condition should go on the RUSP or be added to a State Panel could be improved with data about ELSI. And so we wanted to encourage scholars to include ELSI research in their pilot studies. And so we wanted to make sure that the clinicians, advocates, investigators who were doing pilot studies for candidate conditions had some tools to be able to decide: Well, what are the things we should be asking when we go through this.

And we realize that these are linked to the particular condition. So if you're talking about Duchenne muscular dystrophy, well, then, there are going to be questions. It's X-Linked. Well, should we report carriers? Right? We know that's going to be a question that comes up. And so during the pilot study of Duchenne's, we

should be finding out: Well, what happens when you tell people about a carrier condition? Does it help them or not?

So what was our approach? This actually started because we were working with the parent project, Muscular Dystrophy ELSI Workgroup. And as we were kind of going through what the ELSI issues were, we said, well, this is probably true for every coalition that's trying to figure out the candidate condition.

Obviously, the Bioethics and Legal Workgroup for the NBSTRN has been critical. I mean, I think it's really important to point out how essential this group has been over the last decade in trying to clarify a lot of these issues. And they really provided the framework for doing a lot of this.

So our workgroup, then, facilitated a series of professional and public discussions aimed at engaging everyone we could think of in the newborn screening community, to say, well,

what are the issues that we would include in this paper? We had over 100 stakeholders participate in a variety of ways. This also went to the Newborn Screening Public Square, in our allegiance with Genetic Alliance and Baby's First Test.

The list of authors here -- there were many more people who participated, but these are the folks who actually spent a fair amount of time crafting questions and thinking through all the different issues that might arise.

And what were the results? It came down to that there were really two broad of ELSI issues that come up: Those that were related to results of screening, and that those are related to newborn screening programs themselves and the integrity of those programs.

So in the paper, we describe each of these issues in a fairly brief way. But then we also have a list of what are some of the questions and specific hypotheses that a

researcher might include in a pilot study looking at newborn screening more generally.

I'm just going to go through some of these now. So, for example, what are the potential ELSI issues that are related to positive screening? And Dr. Lantos just talked about, well, with Krabbe, if you have a positive, then you're stuck trying to decide, well, should I go through with this or not? My child looks well. They're telling me he has these tests, and they need to have a really serious intervention. Should I do it or not?

As that pilot study's going on, we could easily craft a survey that asks families: What's this experience like for you? And we may find they say, "This is great. We love having the information. We wanted to know. This is very helpful." They may say, "This created horrible anxiety."

Similarly with false positive results, right? So what was the experience like for

families? Did it dramatically change how they think about their child? Does it cause greater cost later on? Does the family, you know, go to the doctor more often because of that false positive?

Some of the early research is showing that no, it actually doesn't. That would be critical information for us on the Committee and Newborn Screening Panels because we know that some of the conditions that come to us have that large false positive rate. If there's research to show that it doesn't really bother families that much, that would be really helpful in our decision-making.

One of the biggest concerns about false negative, of course, is that it may lead to the false idea that that child's not really sick and doesn't have that condition. So, again, that's worth following up. I mentioned before, carrier status has many of the same issues. Do families want to know carrier status of their child or

not? If we knew the answer to that, then we could say, oh, yeah, we should be reporting this to families. So, again, this is the kind of question that could be included. Indeterminate results show up much the same way that carrier status does as well.

When we talk about ELSI issues related to the system, there are questions regarding, for example, resource allocation. For SMA, the cost of treatment is enormous. And so is this something that should be identified early on and sort of thought about in some systematic way as we're talking about the condition?

Health disparities in equity also comes in, for example, with cystic fibrosis, because depending on the kind of way that you decide to do the newborn screening test, there may be populations that are more likely to be identified or less identified.

Also, if we're doing something like an infectious disease, are there certain populations

that would then have a stigma attached by the very test that you're doing? This may not be true, of course, for many of the newborn screening conditions, but it may be for some. So anticipating that, and doing the research ahead of time, makes sense.

Are there implications for public parental trust? And this is something I think that, Shawn, you were talking about a little bit before. As you start heading towards conditions that have less and less obvious case why they should be part of a public health mandate, are we starting to lose trust in the system? And do people say, "Well, I don't really want to do that because it leads me to learn about these conditions that weren't really that important to me, or the benefit wasn't that obvious." Again, asking families ahead of time using different kinds of ELSI methodology can help answer that question before it comes to us here at the Secretary's Advisory Committee.

And lastly, does the condition raise any concerns regarding parental permission, and challenge the ethical or social justification for requiring population-based screening?

I realize that you can't read these slides; I have two of them in a row. But just to show you that in the paper, we listed these nine questions. We talked about the data sources that were available, and then gave sample ELSI research questions.

So, again, as pilot studies are being developed, here's an opportunity to say: Our candidate condition is an excellent condition. So we know we're going to have issues with carrier screening. What are some of the questions we might ask, and how might we answer them early on.

So to conclude, we are hoping that ELSI questions will get integrated in the pilot studies to help us with our decision-making about these difficult issues. And that's it. We think

this will allow policymakers to better maximize the benefits and mitigate the potential negatives.

All right. Can we go to lunch, or do we have discussion now?

DR. JOSEPH BOCCHINI: Well, thank you for considering your stomach when you were putting this together.

So let's have a couple of -- let's have an opportunity for a few questions or comments.

Thank you, Jeff, for putting that together and making a nice presentation.

So I had Cindy first, then Scott -- Carla?

Okay. So Cindy.

DR. CYNTHIA POWELL: Thank you, Jeff, and to your group for a very important paper. Thinking about the health disparity is part of it, and something where perhaps this Committee be helpful for some of these new conditions that are being added, where molecular testing is really

critical as a second-tier test. And the fact that, personally, coming from a state where molecular genetic testing is not covered by Medicaid, and 50 percent of our patients have Medicaid coverage.

DR. JEFFREY P. BROSCO: Right.

DR. CYNTHIA POWELL: So if we don't include that piece in the newborn screening program, and expect, you know, outsiders to do the testing, or not, you know, I just think that it's extremely important that it be included as part of the newborn screening process and not left up to, you know, other ways of doing -- you know, whether it's a second-tier confirmatory testing, what have you.

DR. JEFFREY P. BROSCO: This is Jeff Brosco. I think that's a really good example of how they're -- the public health impact, right? -- how this is -- affect our newborn screening program is something that you want to take into account.

Is it a relatively simple -- we add the test, and it, you know, can be added into the MS we're already doing, or the substantial resources that come to bear either for the state, or may fall on the families. That's a really critical thing. Thank you.

DR. SCOTT SHONE: So this is Scott Shone. So first -- and Beth and I were talking about this before the meeting started today -- unrelated but sort of related to what Cindy just said is I think we need to be careful that we don't try to new newborn screening to solve the issues that are in other parts of the system. So, you know, it's important for equity to be part of what we go forward with, but not try to solve an equity issue and -- you know, to use Beth's words -- the messy medical system or somewhere else to -- because we have our own problems to creative and solve.

But can you go back to your questions -- 8, 9 specifically? And it's my pleasure to be

between you and lunch.

DR. JEFFREY P. BROSCO: I'm fine.

DR. SCOTT SHONE: Perhaps a delightful ambrosia salad.

So related to 8, 9, I'm wondering if, not only for pilot studies, what do you think in terms of -- and this stems from the discussion we just had around sequencing -- and I was going to hold off until we talk about future directions for the Committee.

But I think that as we continue to entertain sort of this new path of disorders and technologies, both whether it's sequencing or our ability to multiplex extremely rare disorders -- so as an individual disorder, it might not make sense, but if we multiplex them, perhaps we have a greater opportunity to find them -- that as a Committee, we really need to start thinking about ways to evaluate those.

But also, as we look at disorders where benefit is questionable or not yet known, but

states do want to add it, that we need to think about recommendations around -- you know, and I'm not the first one to say this -- but is there a need to think about and get ahead of the discussion of splitting the panel into disorders that are historically -- and we can go back and review -- that these are going to be mandated ; they do have clear benefit to early detection, and treatment is beneficial -- versus we're still looking at this, and parents need to be informed?

And I think that, you know, it still has the opportunity -- and I'm not just saying these, you know, population-based pilot studies -- but that I think that we need to not -- to Shawn's point -- it's not in danger what -- the PKUs, the galactosemias, the things like that, that we know has this history -- at the expense of just trying save babies and end diagnostic oddities and be the saviors for the public health system?

DR. JEFFREY P. BROSCO: So this is Jeff Brosco. And it's a good thing we're having lunch

together, Scott, because we can talk about this at length. But I'll just give four quick answers.

One is that the North Carolina group --

And I don't know if you want to say anything more about it, Cynthia --

-- is trying to look at that, right, to some degree. Or can we say, here are the conditions that everybody knows we're going to screen for; that's part of the core panel. And is there a secondary panel? And what does informed consent look like in the perinatal when you're trying to decide these things?

Barbara Koenig and others have done a lot of thinking about is there a deliberative democracy approach to thinking about this ahead of time, rather than trying to -- you know, we usually hear from families who have the condition and are affected by it, in a really powerful voice. It's hard to get the voice of families that aren't affected, and how that fits into

newborn screening.

Jeff Botkin and others have looked as closely as they can at do these sorts of new conditions interfere with other newborn screening? And it turns out, if you give the right kind of education, at least initially, that doesn't seem to be a problem, that people are able to distinguish and sign up for newborn screening, even as you add things. But Aaron Goldenberg, who may have lunch with us, has a lot more information about this.

DR. CARLA CUTHBERT: So Carla Cuthbert, CDC. So as a funder of pilot studies and implementation, funding opportunities, I'm just very curious about the focus here. When you say "Pilot studies," what immediately springs to mind would be studies that are done before conditions are added to the Recommended Uniform Screening Panel.

Are you also thinking that this might be useful for early adopting states, where there's

still those who are well ahead of the pack? Are you thinking that this is also useful for later-adopting states? Because we make sure that the programs, especially at the tail end, are also getting funded for implementation of these conditions.

So, you know, when I hear "pilot studies," you know, it's a very used word in our community, but it may mean slightly different things to many different people. And as a funder, I need to really understand what you think the scope of this actually is.

DR. JEFFREY P. BROSCO: Sure. Jeff Brosco. It's a great question. I think we meant all three, right? And I'm really glad that you're picking up on that because -- I mean, you heard Dr. Lantos, right? One of our best pediatric bioethicist, and he gets involved because of the NSIGHT projects, right, in genetics, and so we have his wisdom that we didn't have before.

Just to give one concrete example: The State of Florida. We just -- in August, we're trying to decide about Pompe. And one of the questions: Are there so many indeterminate sort of late-onset? Is that fair to do? It would be wonderful if in one of the early pilot studies, we had asked families, you know: What happens when you get this indeterminate result? Does it change the way you treat your child? Does it drive you bananas? Does it increase your anxiety? Does it raise parental stress? Or does it like, "This is great. Now we know. We're ready for anything. When the earliest signs come, we're ready to handle this."

If we had that sort of documentation, it would be much easier to decide about Pompe. That would sort of be -- you could scratch that off the list for reason not to add it to the State Panel.

DR. SUSAN BERRY: So this is Sue Berry. Thank you, Jeff, for summarizing the work that

that fantastic committee was able to undertake. I think Carla's question about what kind of pilot are we talking about is part of our problem.

It has to do also with this whole change in the understanding about when you're using spots when it's research -- the common rule and how that has really impaired, I think, our ability to make the distinctions that we properly should make about a pilot that's trying out a new test and a pilot that's implementing something we already know how to do, which you have to frame in the right context.

And those are completely different things and, in my view, carry very different responsibilities. You're talking about Florida trying to decide about implementation. And in other cases, we're talking about trying to try a whole new disorder and doing a pilot test to see if it works. And those not the same thing; we use the same word.

So really clearly defining that is going

to be super-important. And I would argue that, in some cases -- I'm going to throw a nuance in here; I'm going to look over a Mike a little bit -- because one of the things that we've been also tossing around is the idea that maybe we need to try something out to see if the whole process of screening is effective with a provisional approval of some sort, where we add a disorder and say: Let's try it. Let's do the experiment and see if it works. And then, at the end, you say: You know, this wasn't really a very good idea. We don't really think we should add this permanently.

And I don't know if we're going to be in a position where the research environment will permit that based on the blood spots availability. But that's another nuance that may end up arising.

I'd also point out that Ohio did sort of an experience like this, because when they added Krabbe, they caused it to be an informed consent

activity. Whether their people are really informed or whether they make that conscious decision, the expectation is that people are giving permission to do the screening for Krabbe. And I'm hoping against hope that the people in Ohio will be studying that and sharing that with us as well so that we can see what the impacts of that activity are. So thank you.

DR. BETH TARINI: This is Beth Tarini. I think that's a great idea, Sue, because I think that oftentimes that that sort of is a potentially great compromise, because we're often hearing this zero-one binary discussion -- which we heard yesterday -- which is: This is a rare disorder around CTX. We can't possibly be held to the same requirements of a common disorder of doing an RCT. We're rare. It'll take too long. It'll take too much money. It's just not feasible; you know, it's complex.

But that doesn't mean that it gets a pass, and that we don't get the data that we

need.

I think the answer is somewhere in the middle of, yes, you have a rare disorder. Your numbers are difficult. It will be challenging. But is there a way forward that allows us to have some bit of inching towards additional information that's valuable, as opposed to just opening the door to say: It's okay. Free pass in. We'll accept the minimal and extremely limited data that we have because it's rare. Because if that's the case, and we're screening for rare disorders, then the screening thresholds come way down, because by definition, everything is going to be a rare disorder.

So there has to be a way forward that addresses this issue, and I think that's a very good one, potentially.

DR. SHAWN MCCANDLESS: Shawn McCandless. Sue, I just want to respond to the question about Krabbe in Ohio and clarify that, having just recently moved from there, it's actually not an

informed consent opt-in; it's an opt-out. And they added the lysosomal screening panel, which is three diseases -- Pompe, MPS1, and Krabbe. And one can choose to opt out of those. That is generally not something that is brought up unless the family brings it up. So it's really not going to answer the question about -- it's not going to answer any questions about informed consent and what people really want.

And interestingly, when we tried to organize a clinical trial to evaluate sort of parents' responses to that, and as well as parents' responses to false positives, there was a great deal of push-back. And basically, the legal adviser -- I have to say, the State Lab in Ohio is amazing. They were amazing to work with for the 15 years I was there; they're great. The legal representation for Health and Human Services was less cooperative in terms of our planning our research and asking really important questions.

And I think all of that points to what I would say on behalf of the SIMD is that we are strongly supportive of a mechanism for creating a mechanism for an evaluation phase for new disorders that are being added to newborn screening panels, and doing that in an organized fashion.

And I say that as a group of physicians who spend every day in clinic doing experiments, because we have no data to support most of what we do in clinic. And it would be hard to describe a more unethical way to practice medicine than to do experiments every day in clinic where you don't ask people for informed consent, and you don't explain to them that they are part of a research project because we really don't have evidence to support what we're doing, other than that we believe it's the best thing.

That's a very traditional approach to medicine. But the reality is, today, we are doing experiments in our clinical practice, and

it doesn't feel very nice many times. So creating a mechanism whereby we could have this sort of test period, where we really use clinical care to define whether a new approach is useful or not -- whether it's in treatment, whether it's in screening or others -- is not just a good idea. We should feel required to do this, moving forward, for rare diseases at least.

DR. JOSEPH BOCCHINI: Thank you.

I think with that comment, I think we'll close this session. We would like everybody back at 12:45, so we can start afternoon session on time. I want to thank everybody. I think this has been an extremely useful morning, with lots of good discussion. So let's close the morning session.

Any comments that you need to make?

(No audible response)

Okay. So we'll close the morning session, and we'll see you back at 12:45. Thank you.

(Lunch break)

DR. JOSEPH BOCCHINI: All right. Let's reconvene the meeting. And we need to start with roll call.

So Kamila Mistry.

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Mei Baker.

DR. MEI BAKER: Here.

DR. JOSEPH BOCCHINI: Susan Berry.

DR. SUSAN BERRY: Here.

DR. JOSEPH BOCCHINI: I'm here.

Jeff Brosco.

DR. JEFFREY P. BROSCO: Here.

DR. JOSEPH BOCCHINI: Carla Cuthbert.

DR. CARLA CUTHBERT: Here.

DR. JOSEPH BOCCHINI: Kelli Kelm.

DR. KELLIE B. KELM: Here.

DR. JOSEPH BOCCHINI: And I think Debi Sarkar for Joan Scott.

MS. SARKAR: 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 M. SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini.

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: And Catharine Riley.

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: And then for organizational representatives, Bob 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 Rink by webcast.

(No audible response)

DR. JOSEPH BOCCHINI: Jed Miller by webcast.

(No audible response)

DR. JOSEPH BOCCHINI: Are we okay with the phone lines?

UNIDENTIFIED FEMALE: We're getting a lot of feedback.

DR. JOSEPH BOCCHINI: All right. So just to be sure, Britton Rink and Jed Miller?

(No audible response)

UNIDENTIFIED FEMALE: Yeah. Jed Miller's out there.

DR. JOSEPH BOCCHINI: Okay.

Susan Tanksley.

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus by webcast

(No audible response)

Natasha Bonhomme.

MS. NATASHA F. BONHOMME: Here.

DR. JOSEPH BOCCHINI: Siobhan Dolan by webcast.

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: Cate Walsh Vockley.

(No audible response)

Cate needed to leave early. She was going to try and call in if she was at a place.

Okay. And then Shawn McCandless.

DR. SHAWN MCCANDLESS: Here.

DR. JOSEPH BOCCHINI: Okay. Thank you all. All right. So for this portion of the meeting, we're going to have presentations of the activities of each of our three permanent workgroups, and then a first report from our new Ad Hoc Workgroup. So we're going to start with a report of the activities of the Education and Training Workgroup.

Beth Tarini.

DR. BETH TARINI: All right. So this is our roster, just to remind those of you who is on this workgroup. I know we spoke a lot about

education yesterday, so this will be brief. What I wanted to do is -- we talked about current member activities -- and highlight the robust engagement that we have amongst our membership.

So Yvonne Kellar-Guenther from NewSTEPs talked about a video tutorial that she is working on, which is going to focus on midwife client discussions about newborn screening and will be used as an educational tool for midwives.

And Cindy Powell discussed the Early Check Project, which is the Voluntary Screening Project in North Carolina for Fragile X and SMA that she is part of. Cate Walsh Vockley is working on educational materials as part of NSGC, which will have their annual meeting next month.

Natasha Bonhomme is working on the Newborn Screening Family Education Project, the aim of which is to educate and train parents on newborn screening issues.

Sue Berry and Amy Gaviglio in the Midwest Region have developed the MOC module for newborn

screening.

Amy Gaviglio has a genetic counseling student who's working on a master's thesis about redesigning the newborn screening report and content to improve parent and provider understanding.

Jeremy Penn is working on his master's thesis, which is looking at parent preferences for newborn screening result communication, organization, and structure for the delivery of that information.

I discussed the receipt of my RO1 to study post-screening harms from false positive results of newborn screening.

Aaron Goldenberg has a master's thesis student -- not Aaron himself; he has his master's -- and he presented this data: "Content Analysis of State Newborn Screening Education Materials." He presented the data on behalf of of his student to us, and had an excellent comparison to past studies by Fant et al. I believe Dr. Kemper, if

still in the building, was on that manuscript, and it shows a nice comparison longitudinally between the content of educational materials for newborn screening now and in the past. And that analysis will continue, and then end in manuscript form.

We discussed yesterday the communication guide, which I had shown you. And this is where you can find it currently on the website, under the Report section of the Advisory Committee website, under 2018, under Other Committee Reports.

And the education guide, we discussed yesterday, and will go up -- if not up -- is it up now? It will go up.

UNIDENTIFIED FEMALE: Next week.

DR. BETH TARINI: Next week.

UNIDENTIFIED FEMALE: Next week.

DR. BETH TARINI: Mark your calendars. Next week. You'll have something to do between now and Thanksgiving.

So the Ad Hoc Workgroup. We spent a significant portion of our time discussing the Ad Hoc Workgroup newborn screening results. We have four members of our Committee that are also part of our workgroup -- sorry -- that are also part of this Ad Hoc Workgroup: Myself, Cindy, Joyce Graff, and Amy Gaviglio. And I think -- am I missing anyone?

UNIDENTIFIED FEMALE: Jeremy.

DR. BETH TARINI: And Jeremy Penn. There are five of us. And so we relayed the discussion from the previous hour to our group of the robust discussion we had and that Dr. Baker will present this afternoon. And some issues as we talked about this area to consider that the group thought were important to bring forward were the importance of looking at the definition and harmonization of the terminology used by the laboratory in their reports to providers of newborn screening results. There was concern that including a focus of communication of the

providers to the parents, and that aspect of newborn screening results and the goals of the Ad Hoc Workgroup may be too great to tackle, and that they would await the precision of the action items that would come as the Ad Hoc workgroup worked through its initial meeting, and subsequent.

Questions?

DR. JOSEPH BOCCHINI: So any questions or comments for Beth?

(No audible response)

I don't think I'd want additional activities. Thank you.

DR. BETH TARINI: Okay.

DR. JOSEPH BOCCHINI: Next is the Follow-Up and Treatment Workgroup update. Jeff Brosco.

DR. JEFFREY P. BROSCO: So here's a list of our members.

I first want to thank Kathryn Hassell and Sylvia Mann for being part of our workgroup for

the last few years. We're hoping to keep them and their voices on our group informally as we go forward.

And also to welcome Jed Miller from the Association of Maternal and Child Health Programs as a new member of our workgroup.

So our Quality Measures Report was posted on the website. Hooray. We'll come back to that in a few minutes.

Medical Foods Report -- as you know, we as a group -- as a Committee already accepted it. And because we want to publish it, hopefully in Pediatrics, it has not gone up on the website yet. But Dr. Berry and her team are working hard on getting that done.

And just to sort of recap where we are. So for the last year, we've been brainstorming about what the roadmap should look like. In August, September Drs. Schneider and Ostrander sort of put some preliminary proposals that got our group really riled up and moving. This idea

of a federated system is based on the idea that we want to ensure that every child with a newborn screening condition receives high-quality, evidence-based, family-centered care. And of course, the United States doesn't have a single system, so it kind of has to be federated, and we're thinking about it at these different levels.

We found that it's really helpful, because we only do this every few months, to sort of remind everyone where we've been and how this all fits together. I'll do this very quickly because you've heard this many times. But just remember that 10 years ago, we started thinking about what does long-term follow-up really look like, and we see the key central components and features. And we are following through on this work still.

A few years later, the group looked at those same central components and said there were these different perspectives, and came up with a

list of questions that should be asked. And most recently, Cynthia Hinton and the same group, more or less, published what they called a framework for sharing good outcomes.

So on the left, improved survival and well-being for individuals with specific screened congenital conditions. So what does that mean? Decreased mortality, decreased morbidity, but also growth in function, family experience, reducing disparities. So those are the outcomes we all recognize. And the drivers are diagnosis, therapeutic care, coordination of services, and research. And then you see the kinds of measures and the concepts that was laid out a couple years ago by Cynthia Hinton and the group.

And this is how the Quality Measures Report then fit in. So this just got put on the web last September, but was approved by this group in February. And so, as you all know, quality measure is a crucial part of health and healthcare systems. There's lots of different

kinds of quality measures. Collecting them is not easy, and different perspectives are necessary in order to do that.

We had a bunch of suggestions, but I want to tell you, we have made progress already on some of them. So the first idea of identifying a core set of long-term follow-up quality measures and data resources, both NewSTEPs and NBSTRN together have been working on what are those core things that are true across all conditions. And so this has been really helpful in moving the field forward.

In terms of encouraging the use of a large data collection activity, through the National Survey of Children's Health or HEDIS QI activities -- again, we've already made progress. I think somebody should pause and celebrate.

Through our colleagues at Bureau of Maternal and Child Health -- Joan Scott reported to us yesterday that in the National Survey of Children's Health, we've now added a couple of

questions that ask: Do you have a newborn screening condition, basically? And so this is going to allow us, at a state level -- and some states may choose to even look at the county level -- to see how children with newborn screening conditions are faring compared to other kids with special healthcare needs and the general population. And of course, trying to get our electronic health records to work would make this sort of data collection much simpler.

So just to remind everyone, this is the kind of map that we're thinking about and sort of moving out first. We can do long-term follow-up treatment quality improvement for individual conditions. And those are the newborn screening conditions, and the classic example is something like cystic fibrosis, where each child goes to a center of excellence, and there's a lot of data that's collected, and this continues quality improvement.

At the newborn screening program level,

obviously, states -- both the programs and the Title V folks -- look to see how the newborn screening program is working in terms of timeliness in the short term, but also, many states do look at long term.

Children with these conditions are part of the larger group of children with special healthcare needs. And that's any child who has a medical condition that's chronic and needs more medical care or educational resources than the average child. And then, all children.

And the reason why this is so important, as I mentioned before, is that there are things -- like most Medicaid and health insurance organizations are doing a lot around quality measurement that affects everyday care. So it's not just quality measurement. When our state Medicaid office puts a HEDIS measure, and says, "Are you looking for lead?" This changes practice across our entire state.

So making sure that the newborn screening

quality measures get built into those larger systems is really critical, and that's where the National Survey of Child Health fits in.

And then we hit a roadblock. And there was this moment in our meeting yesterday -- it was a great meeting, lots of energy -- where I realized, okay, I've been co-chairing this with Chris for the last two years, and I don't even know what our Committee means. What are we doing? What's our workgroup doing? And there was this debate about what does follow-up and treatment really mean?

And so one of the issues was that word "follow-up," for me, just means, well, if I'm a clinician, and I'm following someone up, well, if they need treatment, I treat them; if I need to talk to them, I talk to them. That's what follow-up means.

But for some members of the group, follow-up meant "Are we doing reporting?" So follow-up fit into this category of collecting

data and assuring that the kids are doing all right. So we had to sort of unpack that.

And then there was this question about "Does treatment imply equity?" And it sounds like a simple question, but it's actually tricky, right? Because you can think about newborn screening as we set up our newborn screening program, and at least some children are helped by it. We identify some children with SCID, and they get the appropriate treatment, and they do better. But do we have any obligation to make sure every child is identified, and every child gets treatment, and they all do better?

And so if you look at the diagram here, you know, equality is sort of -- there's that branch. We do newborn screening in all the kids; they all get SCID treatment; they all get SCID screening; we refer them all to someone who can do the treatment. But we don't really know what happens in the long run. And maybe some get the apple, and some don't. So what is the

responsibility for long term?

And this sort of then came down to, well, who is the "we"? Right? When we say "Who has the responsibility," where's the "we"? And I've just put together a few examples of what that "We" may mean. And again, it fits in with that diagram from before. So you can imagine, at the all-children level -- I mean, there's Maternal and Child Health Bureau, Medicaid, State Departments of Health. They tend to be saying all maternal and child health is important. We want to reduce disparities. We need to make sure that we do assurance. Yes, every child is getting what he or she needs. And equity: Are we reducing disparities? Are we making sure that kids are all doing well?

Then there's folks who are interested particularly in children with special healthcare needs. This tends to be, for example, state Title V directors. And we have the same kinds of concerns, but we focus on that CSHCN population.

And then there's state newborn screening programs. So what are the limits of responsibility? And Scott was saying this sort of before, where we can't fix the entire healthcare system. So how much do you hold the state newborn screening program responsible for long-term problems with equity?

For clinicians and researchers and family members, clearly, the primary focus is on that individual child: How is that child doing that has a condition. And of course, many feel a much greater responsibility for other children as well. We see that every time we talk about condition, that people come to the podium, the scientists, and families are advocating for a lot more kids than just their own.

So, because we weren't sure of all those answers, I figured we should go back to our charge from 2011, and say: What is it that we're supposed to do? And basically, there's three things: We're supposed to identify barriers,

develop recommendations, and provide guidance on who's responsible.

And if you look, it says very clearly: "Short- and long-term follow-up" -- so it's not just short-term -- and that follow-up is meant to include treatment for any children that has something relevant to the newborn screening results. So identifying barriers certainly suggests we have some responsibility for equity.

And then offering guidance on who's responsible, it says we are part of the group that helps decide what's the "we," and what should the different folks do.

So, based on all that, we come to the Committee with a request, and that, the Long-Term Follow-up Workgroup recommends that we explore what a coalition proposing a candidate newborn screening condition for including on the RUSP might do to assure access to long-term follow-up and treatment.

Let me say very quickly, this doesn't

mean that, you know, if there's not a perfect long-term plan that something shouldn't make it on the RUSP. But we, over the next few months, would like to start exploring what this might mean. Is it just simply a plan -- you know, a blueprint for what could be done to do long-term follow-up and treatment?

And so, for example, that might also be worthwhile asking the folks who propose the condition: What are the key outcomes that matter? For sickle cell disease, for example, we talked about how use of hydroxyurea and transcranial Doppler are two of the most important things for measuring quality in sickle cell disease. There's lots of other things you could measure, but at least when the group of people who care most about sickle cell identify those up front, it certainly makes it easier to do long-term follow-up.

So what are the things that might be included if we wanted to say that a candidate

condition should include those things? And our goal would be to have, you know, a couple of our conference calls, and then maybe provide recommendations for February, when we're looking at our evidence review, or reviewing our evidence review.

And the other thing we would like to keep doing, if it makes sense, is exploring next steps for this sort of federated system. So at the condition-specific coalition level -- so we've talked about patient registries, centers of excellence, how NORD fits in. At the state level, some states are trying to see how they can connected with -- we're still calling them "birth defect registries." But is that one of the ways we can do a long-term follow-up that doesn't take a whole lot more resources.

There's also a NewSTEPs pilot that Marci Sontag was telling us about. So some states might start thinking about what they can do for long-term follow-up at a state level.

And at the level, all the initials that I can't tell you what they stand for, but basically, the Clinic Lab Standards Group is getting more and more interested in what are the standards that should be applied to doing tests -- what's the clinical outcomes.

I mentioned before, HEDIS. HEDIS is driving all of the pediatricians to do lead levels. And in South Florida, there's no lead poisoning, or virtually none. And it's an opportunity cost. Are there ways we can use HEDIS and other things to drive us to do better with newborn screening conditions?

And of course, the electronic health record, and all the regulations that go along with it, should allow us for better access to information.

So I will stop there.

DR. JOSEPH BOCCHINI: Thank you.

Questions or comments?

Sue, and then Melissa, and Beth.

DR. SUSAN BERRY: Sue Berry. Mine's only a minor one. The concept of not just long term, but longitudinal.

DR. JEFFREY P. BROSCO: So this is actually an interesting question. Should we be thinking about the name of our group, since apparently, I didn't understand what it meant?

DR. SUSAN BERRY: Well, it never says anything about, you know, long-term in the --

DR. JEFFREY P. BROSCO: Right.

DR. SUSAN BERRY: -- you know, anyway.

DR. JEFFREY P. BROSCO: And a better word might even be "lifespan." That's a word we've been using a lot in our MCHB work, because lifespan implies that what happens for a baby matters through the lifespan. It kind of gives you a little bit more wiggle room. So we might think about what are the right words that we want to use to name our workgroup in such a way that we all know what we're talking about.

DR. SUSAN BERRY: So this is Sue again.

I think just calling it the "general workgroup," "follow-up." But I think what we're talking about is the sense of responsibility we have in the system to assure the promise of newborn screening.

DR. MELISSA PARISI: Melissa --

DR. CHRIS KUS: This is Chris. This is Chris. When you get the chance, I want to make a comment.

DR. JOSEPH BOCCHINI: Yeah. Go ahead, Chris.

DR. CHRIS KUS: Yeah. I guess the comment relative to this is we have, through the work of the Committee, defined "long-term follow-up," so at the very least, we want to be able to deal with long-term follow-up. And if we want other things to be in the Committee's purview, that's fine.

DR. JOSEPH BOCCHINI: Thank you.

DR. MELISSA PARISI: Melissa Parisi. So I have a question about the extent of long term,

because I didn't actually hear you define it. And I know that there's a lot of confusion about, really, what long term means. And it seems like, you know, for some groups, five years is long-term follow-up; for others, it's the whole life span; for others, it might be three months after the blood spots are thrown away.

So I'm just wondering whether there's any sort of way of sort of wrapping your hands around this temporally, because in part -- I'm asking this sort of for a selfish reason as well as for a philosophical reason. You know, we -- and I support the longitudinal pediatric data resource as part of the NBSTRN, and we're always trying to be careful about where our duty begins in comparison to the shorter-term follow-up responsibilities that tend to be under the purview of NewSTEPs and APHL.

So I'm just wondering if your Committee wrestled with this and came up with any conclusions.

DR. JEFFREY P. BROSCO: No.

DR. CHRIS KUS: This is Chris. I'd make a comment again.

DR. JOSEPH BOCCHINI: Go ahead, Chris.

DR. CHRIS KUS: Yeah. I would refer people again, if we have this discussion -- we did do a paper on long-term follow-up, and our definition says that "Long-term follow-up comprises the assurance and provision of quality chronic disease management, condition-specific treatment, and appropriate preventive care throughout the lifespan of the individuals identified with the condition included in newborn screening."

DR. JEFFREY P. BROSCO: That's a much better answer than mine.

DR. JOSEPH BOCCHINI: Thank you. That's a good --

DR. MELISSA PARISI: But when does it begin? So at the time of you're given the diagnosis?

DR. JEFFREY P. BROSCO: Yes.

DR. JOSEPH BOCCHINI: Okay. So I have Beth and --

Or Sue, did you want to answer that specifically?

DR. SUSAN BERRY: This is Sue Berry. I wanted to comment that one of the things that -- as we are working on the concept of what is short term and what is long term, those distinctions are blurring pretty heavily when you have disorders that when you diagnose them the moment you get them, whatever's going to happen is years in the future. I think we should be thinking about the continuum rather than trying to draw a line about what's short and what's long. I mean, that's why I was careful to mention that there was something beyond long versus short, but longitudinal.

DR. MELISSA PARISI: Okay. Sorry. Melissa Parisi one last time. So I completely agree with you. And it isn't like there's a

hard-and-fast division. The problem is that sometimes our federal mandates are a little more black-and-white than we think they should be. And so I'm just asking for the purposes of trying to help clarify our various roles as federal partners in this.

DR. JEFFREY P. BROSCO: Sue?

DR. JOSEPH BOCCHINI: Jeff, then Mei.

DR. JEFFREY P. BROSCO: Jeff Brosco. Just one thing. So you as a -- or we as a Committee could task our workgroup to look at this a little more closely, if you think this would be useful. I mean, it's something you could ask us to do.

DR. JOSEPH BOCCHINI: I certainly think looking at the current definitions that we've been using in the publications, and then seeing if they're still valid or need to be clarified further, based on what Melissa and Sue have indicated, I think is certainly reasonable.

DR. MELISSA PARISI: Two things. To

Sue's point, the promise of newborn screening, and I think potential low-hanging fruit for this workgroup, is the diagnosis of congenital hypothyroidism, because the diagnosis of congenital hypothyroidism, and what is used to diagnose it, actually have significant relevance -- and Mei can speak to this, I think, as well -- for how you set your cutoffs in the screening laboratory.

So, in fact, it's also an example of where follow-up -- whichever you call it, short or long -- follow-up has actually direct relevance on the screening, because I think sometimes we think of follow-up as like someone else's job. It happens. It's about quality of following up the child. But this is an example -- it might make an example potentially, but maybe not -- of where if we can get a handle on what the follow-up is doing in terms of the diagnosis -- this issue of the rise that some states have seen in the prevalence of congenital

hypothyroidism, then it can help guide the screening cutoffs set at birth.

DR. MEI BAKER: Right now, we largely follow CLSI documents in terms of definition, what's a short-term follow-up, because I do short-term follow-ups, so I'm more familiar with that. It's basically is the screening-positive cases that has definite conclusion means the false positive, true positive, then the kids has been in the care. Done. But I also agree, we shouldn't have this clear drawn line. Just like Sue was saying, the new condition, the diagnosis, obviously, can be a long time. And I feel -- get back to Beth was saying -- I think important newborn screening program needed to have this short-term follow-up. But the frame -- the reason is that they direct allowed us evaluate how our tests performed. I think it is important.

And also, what Beth was saying is, for example, congenital hypothyroidism. At the

moment, we are right. But the kids -- one year later, we don't know. But it can be -- but that data will impact the improve on design and the stuff. So I think that's the way I see it.

DR. SUSAN BERRY: I would comment that the CLSI document that you're referencing is in revision. And some of the comments -- part of my conversation here reflects some of the discussion we're having about thinking about those in a little more subtle ways, and recognizing this continuum as representative of how we do things, as opposed to sharp points of definition.

I understand why sometimes you have points of definition you have to cut through. And then some people say, well, it's the point of diagnosis that's the switch. But now that we don't have as clear a time when a diagnosis is made, really hard to even use that one. So we really tried to think about that very hard as we write some of these guiding documents.

DR. MICHAEL WATSON: Mike Watson. So I

think it would be good to capture -- you know, to what end are you capturing long-term follow-up data? You know, it really is to understand whether you're realizing the outcomes that are why you decided to screen -- you know, it fits in with why we worry about timeliness, because presumably, if things aren't timely, not everybody's reaching the same outcome as the place that is timely.

So I think capturing why you're doing long-term follow-up data collection either needs to be in the definition, or it could even be part of the title, because there has to be an end that you're trying to realize.

DR. JEFFREY P. BROSCO: So this is Jeff Brosco. And that's actually what we -- this is the problem with the "we," right? So, yeah. For a state newborn screening program, they may be mostly interested in program quality assurance. Yeah. Are we identifying kids, minimizing false positives, you know, minimizing false negatives,

making sure that we connect children to clinical care.

For a state Title V director, oh, I want to know much more. I want to know how that child's doing over time, for much longer than just the newborn screening program. The "we" matters, and so that's the question: Is our federated system -- we think the best way to do it is that all these four levels just keep nudging things forward, because some protagonists in this will have different interests. And that's okay.

DR. MICHAEL WATSON: Yeah. But I think identifying that shared interest, which is realizing the best outcome for the baby, is what pulls everybody together.

DR. JEFFREY P. BROSCO: Exactly. And that's why even at the all-children, right, which is furthest away from newborn screening -- we have an example of how, through the National Child Health Survey, we're able to improve

newborn screening.

DR. JOSEPH BOCCHINI: Okay. Other questions or comments?

(No audible response)

I think relative to number one --

DR. JEFFREY P. BROSCO: Yeah.

DR. JOSEPH BOCCHINI: -- the first one about the RUSP -- and certainly, as we're going forward with the reevaluation of the nomination packet as well as evidence review, this certainly is a topic that can be looked at broadly during that review.

DR. JEFFREY P. BROSCO: Great. Thank you, Joe.

DR. JOSEPH BOCCHINI: Okay. Other questions or comments? Scott?

DR. SCOTT M. SHONE: Scott Shone. So just to add on to that, I think that, at least the sort of feedback that I have heard -- and so this is personally to nominators who, obviously, after a disorder's added to the RUSP, we're

thrilled that they made it through this process. I think they sort of feel like there's this drop-off of as, then, it goes into this national implementation -- I think that perhaps we should talk about ways to engage them to help diversify the workload over time for some of these topics, so that maybe the -- you know, sort of the -- what I've heard is their journey doesn't end with the RUSP. Although, I think a lot of people thought it would, and then they realize, wait, there's still a lot more.

And so if we can engage the nominators from nomination, as we talked about yesterday, with CTX and helping refine that nomination all the way through to implementation once an disorder's on the RUSP -- so this might be broader than just what you're talking about, Jeff, is --

DR. JEFFREY P. BROSCO: Agreed.

DR. JOSEPH BOCCHINI: Okay. Good.

DR. JEFFREY P. BROSCO: Annamarie.

DR. JOSEPH BOCCHINI: Annamarie.

MS. ANNAMARIE SAARINEN: Annamarie Saarinen. I just want to say that for, like, SCID -- and CCHG is sort of like in a different bucket. But I think there are, certainly, many advocacy organizations and scientific organizations that have been very concerned about, like, just because it got added to the RUSP, now we shouldn't pay attention to it anymore. We want to see at what point we had -- like for each of the different conditions we're identifying, like what does that mean for them? Or does the earlier identification actually improve their outcome, because they were -- accessed surgery faster versus not, etcetera, etcetera. So there's that.

But I would say the family advocacy and research organizations around SCID have also done a remarkable job of that. They definitely did not just drop off after things were put on the RUSP. So maybe those are just like pathways

that, you know, we look at and say, like, that's a best practice; how do we leverage.

DR. JEFFREY P. BROSCO: Right.

DR. JOSEPH BOCCHINI: And we've actually talked in the past about leveraging organizations like the CF Foundation and others that might have databases and -- so that looking at outcomes related to specific disorders where that data might be available is another way to enhance what we do.

Okay. All right. Thank you.

Thank you, Joe.

All right. Next is the report from Laboratory Standards and Procedures. Kellie Kelm.

DR. KELLIE B. KELM: All right. Good afternoon. We had a great meeting yesterday. And so we had a couple short updates, and then we spent the majority of the time brainstorming new topics.

So first, I just want to thank our

workgroup. And we were happy to have pretty much everybody except for a handful of people there in person, which was great.

So I should go back real quickly. And so, as you know, we've spent a lot of the last few meetings -- it's been three or four or maybe more than that -- doing a lot of work in our workgroup on that risk assessment and cutoffs topic. You know, the Committee asked us a lot of information. We were working with APHL, so a lot of our time was having discussions about the early framework and the drafts, and then some other information the Committee asked us to consider about recommendations and suggestions, etcetera.

So although we have -- and what I'm going to plan to do here is sort of go over our original workgroup charge, and the last two projects that actually had been sort of reapproved the last time we, as a workgroup, sort of went back over our projects.

A lot of topics had come up, whether it was in a workgroup or even in the Committee, and we wanted to propose -- and Dr. Bocchini suggested that we propose some of the topics that have come up into sort of some cohesive topics -- bringing up the two products that we sort of had, decide whether or not, you know, those are still things we should work on, and then the new topics, and then see whether or not the Committee has any input on what they think the workgroup should be working on, since we're sort of at this break.

So this is our charge: Define and implement a mechanism for the periodic review and assessment of conditions on the RUSP, the lab procedures utilized for effective and efficient testing, and infrastructure and services needed for effective and efficient screening of the conditions.

Now, as I look at some of the topics

we're even talking about, some of these may even fall under number 2 and number 3 already.

So these will be two projects that we re- approved -- I think this was spring of 2017; I'm trying to remember the time we did that. But one of them was "Explore the role of NGS in newborn screening." And so we have had a couple presentations a few years ago, for example, for -- some of the states have given us updates. We've heard from the APHL Molecular Subcommittee on some of the work that they had been doing and some of their meetings.

And so we have gotten updates on this project -- not recently. And a lot of it really is -- some of it is state-by-state activities that they're doing. And so, you know, that is here; we can continue to talk about it. But it was something that I found the topics for us were a little sporadic.

So Project 2. If you recall, our workgroup did the work on the assessment of

timeliness back a few years ago, with surveys, making recommendations that the Committee did adopt. And so it was decided that the workgroup could go back and look at some of the timeliness data as it became available and sort of assess -- besides looking at the data and how successful states were doing.

Some of the questions: What were the implications of early specimen collection, because you know, we knew that the recommendations were going to move it earlier. We already knew California was moving it earlier on their own process. And then, what are some of the unforeseen consequences and cost of timeliness.

So I know our workgroup in the Committee has gotten some sporadic updates from NewSTEPs about the data, and I know they regularly come here. But we haven't actually delved into any of the other questions or see whether or not states are making any assessments, for example, for the

implications or consequences. So we haven't, I think, gotten back to this for a while.

So just to start -- so those are the two projects that our workgroup was approved for, but that because of the risk of us having a cutoff document, we had not gotten back to -- okay.

Now, we briefly did get an update from APHL on their overview of cutoff determinations and risk assessments methods document, and the full name is there in the first bullet. So they had obtained all that feedback from multiple parties. We discussed it in our workgroup; the Committee had discussed it. And they had finished taking all those edits and comments and had finalized it.

The document has now been posted to APHL's website, and they consider it a living document, although Jelili said that they probably won't be updating it anytime in the near future -- that's not their plan -- but that it could be reviewed as needed in the future. I don't have

the link here, but I know if you want to bug Jelili or anybody, I'm sure that he would be more than happy to share the fact that this resource is now available on APHL's website.

And we, similarly to -- Beth did talk for a few minutes about the Ad Hoc Workgroup. Right now we have, I believe, three members, so Mei Baker is chairing it. We also have Scott Shone and Susan Tanksley serving on that as well from our workgroup. And I know some of the things that we talked about, even for our workgroup, and I think some of the information that we thought about might help the Ad Hoc Committee, but I think we still need to be careful that we're not overlapping.

So we had four topics that we thought of. Some of them were a little bit more hashed out in terms of even what the potential product is, so I'll preface it with that.

So topic number 1, actually, is sort of a big umbrella that we think we can fit a lot of

things under that we talk about pretty often in our group, and that's improving specificity of screening. And the things that we really have most often been talking about is, for example, assessing adding variables such as weight, age, and other variables into risk assessments -- i.e., primary screens -- to improve specificity.

So, you know, a lot of states are looking into this. This is some of the information that the CLIR tool can give you. The idea is that you can decide whether or not it actually improves screening. And so I think we're starting to get more data on that that we could potentially discuss and share besides just a simple biomarker test or ratio. You know, are we going to be able to see data where some of this information being added into our risk assessment actually improves specificity.

Number 2 would be new second-tier tests. So we have both molecular mass spec-based tests that are being developed.

And then one of the questions is use of reference labs for second tier, and that could potentially be discussed.

And you could envision that we could put other things under this. And this topic could also fit under our existing projects already, or the charge of the workgroup.

Topic 2, unifying definitions for NBS. And this comes up often, and it's also come up with the workgroup, the need for unified terms for describing newborn screening. So is it normal? Is it negative? Unaffected in range? You know, would it really be in our interest to try to, you know, make a single unifying language that we all tend to use to make it clear, and that we can share information across. And we've heard the same thing. Some of the examples are incidental findings or things like that. And then, obviously, should it be a risk-based description.

So, you know, obviously, we're thinking

about this from the lab perspective, but that has come up numerous times. And I think, you know, we've also heard this issue come up with other things like case definitions. So that was topic 2.

So topic 3 is another thing we -- we had a lot of discussion with even the cutoffs and risk assessment discussions, so we keep bringing it up, because what is the target of screening? What are we likely to find in addition to what we are screening for? We had a lot of discussion about the fact that states should be transparent about what their targets are for screening, because different states do actually screen for different things, and they do that often purposefully.

And so there was some discussion about whether or not -- you know, like SMA, we actually defined that it was for the homozygous deletion. It was defined as we described it in our letter. And we haven't done that for everything. And it

may even make sense -- I guess the question is if the Committee feels there is a need to go back and even look at our list of primary and secondary conditions that are on our website, and assess those and assess whether or not they're clear and transparent -- you know, the core conditions versus secondary targets, defining the target, and then making sure that we're -- you know, we could use this to economize screening for the target.

So topic 4 is one that I definitely think has come to the forefront with some of the things that we've added to the RUSP more recently. So this is the impact of broad phenotypes on laboratories. And you could say genotypes as well, but really, it's more broadly phenotypes.

And so as states start to screen for Pompe and SMA, as they start to bring that on, our idea here is that the states could share lessons learned, especially when they're talking about identifying late-onset Pompe disease. You

know, what's going to happen as we identify SMA cases with two, three, or four copies of SMN2. You know, how are states defining these? How are they, you know, returning these results? How is this going with short-term follow-up, etcetera, because we do think that this is an issue that labs, obviously -- it's sort of new to lab in some ways, that it's -- you know, doesn't happen more often. Can we even take lessons learned from conditions we already have and sort of apply that here?

And the question, whether or not we ever want to get into that or the Committee would be interested in, is whether or not that information could potentially be helpful to refine the target of a RUSP condition, especially as these things roll out.

So I hope I described it well. If anybody from the workgroup wants to speak up and help, that'd be great. But these are the four topics. And I didn't know whether or not the

Committee had any insight on to what they thought -- where the workgroups -- or any other ideas.

DR. JOSEPH BOCCHINI: Thank you, Kellie.

Let's open this up for discussion.

(No audible response)

Well, I'll start with topic 4.

DR. KELLIE B. KELM: Uh-huh (Affirmative).

DR. JOSEPH BOCCHINI: I think this is a really important topic. And certainly in the -- laying out a plan for reviewing those conditions that were recently added to the RUSP by the Committee -- or by the Secretary at the recommendation of the Committee -- we need to have what kind of impact they've had on not only the laboratories, but then down the road with the short-term, long-term follow-up.

So I think that, since that's a project that we're going to kind of get underway, that perhaps there could be some interaction between -- as that project gets started -- your group

helping ask the proper questions, or including those questions, and then evaluating that as that evolves. And so I think that's an important thing for the group to consider.

And the other thing, in terms of timeliness, again, we've got a broader look at that, I think, going back and looking at the APHL data, which represented a group of states, would be good. And then coordinating again with questions and specific information back and forth as that project evolves -- you should be involved in that as well.

DR. KELLIE B. KELM: Okay.

DR. JOSEPH BOCCHINI: So I think those are two things that I think would be important topics to follow.

So let's open it up further. So I've got Melissa, Beth. Who else? Okay.

DR. MELISSA PARISI: Melissa Parisi. So with regard to topic, the impact of broad phenotypes on laboratories, I couldn't agree more

that sharing best practices, sharing experiences among the states is really critical and very important, particularly for many of these conditions that have later-onset phenotypes.

And to that extent, some of this is happening -- perhaps not exactly in the way that you propose, but the Newborn Screening Translation Research Network supports monthly -- and in some cases, bimonthly or quarterly calls -- amongst the clinicians, the laboratorians, and the screeners who had the experience with potentially early adoption or some of the more recent conditions added to the RUSP, and then invite the other states and other representatives and basically anyone who's interested to participate in those calls.

And I think those are a really valuable way in which some of the information about early experiences gets shared, including trying to anticipate and identifying and realize how to handle the later-onset disorders.

DR. JOSEPH BOCCHINI: Melissa, would that information be organized in a way that it could be presented to the full committee as it evolves?

DR. MELISSA PARISI: I'm looking at Mike Watson.

Mike, do you want to say anything about this and how that could be promulgated or presented to the Advisory Committee?

DR. MICHAEL WATSON: Oh, I don't know. I mean, it's a big -- I think it's a significant problem. It's not just phenotypes; it's actually genotypes -- because if you look at -- it's what's coming in the sort of Phase 2, Phase 3 clinical trials of new drugs. We already see it in Duchenne muscular dystrophy, where a pilot's -- should be starting, you know, several months. But it really only targets 15 percent, 20 percent of the patient population. And that's the only group that we will have outcome data on to know that it was worth screening in the first place.

So, you know, I think we are going to

have to revisit not just the breadth of phenotypes, but the breadth of genotypes that are now getting targeted with treatments. You know, the exon 7 deletion is one type, but there's 5 percent that have lots of other kinds of genetic variants in the gene.

So, I mean, I actually think we're at a kind of a paradigm shift in how we think about all of this, and you know, to manage the capacity issues that are coming both on hitting the workforces hard -- the amount of stuff that's in the pipeline is really quite remarkable. And I think it's probably worth having -- you know, really talking about what's coming at some point, because you're always going to be reacting if you don't get a better sense of what you're trying to collide with later, because there's a whole new set of problems, I think, there -- or issues that are coming down the pike.

DR. MELISSA PARISI: Could I follow up with just a comment? Melissa Parisi again. So,

you know, I think just to take a bite out of one chunk again of that, because a lot is coming down the pike -- but to actually say, okay, here's been the experience of having these monthly calls among those who are actually struggling with some of these issues. And I don't know if there's a way to organize that information but I know Amy Brower's been very involved in those workgroup calls and might be able to put something together that would be informative for the Committee.

DR. MICHAEL WATSON: They all go through the same general pathway. You know, we start with just the newborn screening labs when the pilots get going and we're doing with the analytical issues. But then the clinicians that are in follow-up start to realize that there's a lot of things they have not -- that we didn't know was the disease.

You know, we have a tremendous bias of sick people coming for care, and we define these diseases around the sick people. But we lose

that entire mild end of the phenotype spectrum, and clinicians are now starting to wonder, you know, is this the disease? Is it a non-specific finding? Is it going to be penetrant or not?

So there's a lot of things that could happen in this sort of two-stage provisional, final approval process, where you can actually build a lot of information, because we obviously don't know much about what happens and the population level, until we go to the population level, and where your ascertainment of people is unbiased. When you start with sick people, you get a pretty warped view of what these diseases are.

DR. JOSEPH BOCCHINI: So I think it'd be great if we could capture some evolution of what's happened in states that have been early adapters, and whether that's modified the approach and sort of help standardized the approach. That would really be good feedback, I think, for the Committee to understand the impact

of the decision and some of the things that were not really anticipated when the decision was made.

DR. MICHAEL WATSON: Yeah. And since I've been outed so many times, we're going to try to finish this manuscript that has all this stuff in it by the end of the year. It's been, actually --

DR. JOSEPH BOCCHINI: Okay. That's fine. We can invite you back to present --

DR. MICHAEL WATSON: -- for a very long time.

DR. JOSEPH BOCCHINI: -- when it's in press.

Okay. Sue.

DR. SUSAN BERRY: So this is kind of what I was trying to ask a little bit. This is Sue Berry. And I was asking a little bit yesterday, when we heard the presentation about CTX -- and reminding everybody, every disorder that we've ever looked at has an iceberg. We've always

looked at the tip, and then, when we really do it, we see really what the spectrum of disease is.

And I think we should count on that being the expectation rather than being surprised every time it happens. It's like, oh, my goodness, once again. And so, surprise. And so that's an element that really should be accounted for as we plan, not like what have we done -- because each one we've added like that, we've sort of acted like we were blindsided by mild forms. And we knew they were there. And in this case, I don't know if we know that about CTX, but I'm going to be surprised if there's not.

And so it speaks also to this concept of what is a pilot? Is a pilot the experiment that goes before, or is it the implementation of new disorders? And what formal -- I mean, those calls all began as way people could put their heads together so they didn't screw up.

But I think we should really not just

have them be reactive but proactive; they should be part of the process as well, and as part of that continuing quality assurance activity that labs want to do, and that we should be investigating scientifically as well.

So I just think they're really valuable. I know it sort of started with the SCID, and then it was so valuable for that that everybody did other ones. But they've been really fundamentally important to the people who are engaged in them as far as I can tell. So thank you.

DR. JOSEPH BOCCHINI: All right. Cindy.

DR. CYNTHIA POWELL: Cindy Powell. Under topic 3, similarly, some of these other conditions that we're picking up, you know, while screening for the core conditions -- and I'm thinking about the Zellweger spectrum disorders that we're detecting with the X-ALD screening -- which, you know, these much more severely affected patients, which is adding a whole level

of complexity to the, you know, follow-up for these patients that screen positive.

DR. JOSEPH BOCCHINI: Other questions or comments?

(No audible response)

So I just have an additional question. Last meeting we talked a little bit about one-versus two-step thyroid screening for congenital hypothyroidism.

DR. KELLIE B. KELM: Yes.

DR. JOSEPH BOCCHINI: Is that something that you -- of course, I know we did talk eventually to have -- when we had time, have some presentations related to that. Is that something that --

DR. KELLIE B. KELM: So yeah. So I think Beth Tarini brought it up and said, number one, it appeared the prevalence was actually increasing. But I mean, the questions that she had were bigger than the lab group, because she talked about short-term and long-term follow-up.

So I think we started to think about it a little bit, but then, I mean, I think it's a -- right now, it's -- there was such a big bite, there was not one thing that we could think about for lab standards. So I can tell you, we've already heard, you know, CDC's effort years ago to look at one-screen versus two-screen, where CH was one of those things. And the answer was pretty gray.

And so I'm not sure -- it would be interesting maybe to think about whether the Committee wants to invite people to put sort of a cohesive panel together. But I don't think us as -- and CLSI is actually working on a guideline for CH screening. It is still in the -- they have put together a draft, and the Document Development Committee is actually now in the midst of calls to work through the draft. And then I think the idea was -- they're talking about fall 2020, which seems long even for CLSI's -- I thought that they had truncated their

process.

But you know, I still heard that that's probably going to be a guideline, just pointing out the different ways that people do it, not a standard telling people how to do it. So I'm not sure how informative that's going to be. But you know, we didn't have an idea that we thought that the lab group could -- then ourselves can put the project -- but I guess that we can -- if somebody had an idea, that's great. I think Beth's idea was a little bit bigger than just us, so --

DR. JOSEPH BOCCHINI: Right. Yeah. And I was talking more specifically about one- versus two-screen.

DR. KELLIE B. KELM: Yeah.

DR. JOSEPH BOCCHINI: But certainly, that's another important question as well.

DR. KELLIE B. KELM: The lab people just shake their heads and almost don't want to touch it.

DR. JOSEPH BOCCHINI: Okay.

DR. KELLIE B. KELM: Carla.

DR. JOSEPH BOCCHINI: Well, that's a reasonable answer.

DR. KELLIE B. KELM: Maybe Carla wants to add to it.

DR. JOSEPH BOCCHINI: Okay.

DR. CARLA CUTHBERT: But I don't really want to touch it, because I think the point -- the point that came up -- Carla Cuthbert here -- was that, you know, what would be the end goal of that. You know, it would be very difficult to convince a one-screen state to do two screens, or to convince a two-screen state to go back to one screen -- to go to screening just once.

So, again, if it's just educational, to show that, you know, you do pick them up or something like that, that would be great. But the outcome that you're looking for would need to be named very well.

DR. KELLIE B. KELM: And this is also a place where I think, from talking to the state

public health lab folks, is that their targets for screening are different. Some states actually screen for a very limited, you know, spectrum in CH, and some are -- their target is more broad, correct, Susan?

DR. SCOTT M. SHONE: And this is Scott Shone.

DR. KELLIE B. KELM: Okay.

DR. SCOTT M. SHONE: That was actually what I wanted to say. So I think that CH is an example of something that covers, I think, multiple on these topics, but target of screening is one. Michelle Caggana's not here now, but we were talking about this yesterday before she left, that they're looking at in New York is should they just be picking up primary hypothyroidism? Should they be looking at central hypothyroidism?

And that goes into not only where your cutoffs are, but one-screen, two-screen. A lot of the discussion -- at least the publication,

you know, around the one-screen, two-screen is not necessarily that the two-screens found something that should have been picked up on one, but -- on the first, but necessarily, there were other targets that were found -- and CH -- simply realizing as opposed to other --

So I don't want to go down the -- I don't want to touch one-screen, two-screen either, but I think CH is an interesting topic because it covers a lot of these -- you know, defining the terms -- you know, what is the target and all these other things.

So, I mean, it's possible. I mean, I'd like to just -- to be honest, if I could pick something and like work on it and have an outcome. And so love the definitions thing because I think it covers everybody. But I think that if we can identify -- whether it's the most recent disorders, or even -- there's so many lessons to learn from the other 50-something or whatever disorders that states screen for.

DR. KELLIE B. KELM: Or the ones that have been on for 40 years.

DR. SCOTT M. SHONE: There you go. So -- right. And then, and pull forward so that Sue can stop being surprised when we have something occur.

DR. KELLIE B. KELM: Well, and I guess the problem is, when we often initially put these on a list, it is just this broad thing, because we don't know what we're going to get. So I guess the question is: Do we go back and define it? But for example, for CH, can we do one definition? Because states have chosen to actually screen --

DR. SCOTT M. SHONE: Right. Well, I also think that the mercy of the endocrinology consultants in the group. So an endocrinology workgroup in Florida might say something different from Jersey and North Carolina or whatever, that we want to find all of this; or no, we only want --

And so inherent in all this is that's going to happen. You know, newborn screening is state-based public health, and it's wonderful in one sense, and it's challenging in another with everybody who wants to be in the -- so I think this Committee can make recommendations, just like we do on the RUSP. But I think our recommendations need to be more than just disorders, but perhaps what and how.

So, you know, based on this, I'm not saying should recommendation that only primary hypothyroidism be screened for. Or maybe it is. But I think that we should pick something and talk about it and come up with a recommendation, or just say there's nothing here, and that's what --

DR. JOSEPH BOCCHINI: Thank you very much.

DR. KELLIE B. KELM: All right. So it seems like timeliness -- topic 4, and obviously, the others --

DR. JOSEPH BOCCHINI: Continue on the way, right.

DR. KELLIE B. KELM: All right. Thank you.

DR. JOSEPH BOCCHINI: Thank you.

All right. Next is the first report of the Ad Hoc Workgroup, "Interpreting Newborn Screening Results."

Mei Baker.

DR. MEI BAKER: Hello, everybody. I try to get done quick, so everybody can be -- but I think it should be somewhat as a little bit easy for me because -- see, this is a bad one, short -- but it may be easy for me because this has been mentioned many times now. It started with Dr. Bocchini talk about a rationale why we need an ad hoc group, and even mentioned the charge. Then both the Laboratory Group and the Follow-Up and Treatment -- Education and Treatment Group -- I mentioned that.

So first I just want to put that our

members here, you can tell this is a collaboration featuring Laboratory Subcommittee and the Education and the Follow-Up -- no, Education Training -- the subgroup together.

Just kind of remind the people in terms of this workgroup, the charge -- and that we had the first meeting yesterday morning, and then we talk about the components of what we do want do, how we disseminated that. So here is the -- we have two parts.

First we want to achieve is newborn screening result interpretation. Component of this is multiple components in that I feel a lot of work has been done trying to educate the primary care physician newborn screening is a risk assessment; it's not that -- it's a tool. But I think we want to do is to base on already being done, a little bit further to embed all these concepts, the ideas into their day-to-day practice.

So we start think about a -- let's just

start with the laboratory, how we put it on our report. So if we have a concept risk assessment, let's describe that way. So now we generally -- we have a -- people talk about the terminology combination. Yeah. We want the harmonization. And our group want discuss more. You call normal -- have a normal, positive, and negative.

And I still think -- it's my personal opinion -- we still -- laboratory -- you still have in the middle ones. And Jeff mentioned that: Indeterminate. So I think we need to find out. And this will be discussed in more detail.

Another things is why we have the joined group. And then you put a language -- language can really communicate the message you really want to give, so we need be mindful for that, and we have a lot people have experience on this workgroup, so we have help us.

Another things, a concept is, as a laboratory practice, you call the abnormal or positive where you have interpretation and

recommendation, but we feel strongly -- even, quote, unquote, a "normal" result, we still want have a language in place -- interpretation -- what a normal means, what a screen letter means. And so I think it will be embedded in that.

So the second piece is, based on the APHL CDC worker -- QIQC worker group -- and Kellie already mentioned that -- it's an overview about a cutoff documentation. And this worker group will be reviewed more extensively, and also, based on that, come to some recommendation in terms of the policy regarding how you establish cutoff, how you do the ongoing evaluation. So that's the two things that we will work on that.

So the details still need to work out, but the certain action items that has been discussed is: One, you have the language or have a description how you communicate with partners, because I think we're trying to tell primary care physician what to -- is better their own organization to recommend it, or to, you know,

promote that. So we talk about a potentially organization, the APA, AAFP, and APHL, and CDC, and that largely, for APHL, CDC, we'll work through QIQC Committee, and then we'll even talk about including some members from that worker group subcommittee.

And so that's actually interesting, because in our worker group, like Sue Berry there, you know, she had a connection with AAPP. I know she's going to try to promote this concept in a consult meeting. So it will help us to test out, you know, how much support we can get from that organization, and how much we can get their endorsement.

So second part is develop the recommendations. So this language is a two-part, is why is the part 2, our charge -- we hope we can get us some recommendation. And for the part 1, we will develop some language, report language, and also writing up some white paper or some peer-review publication. The purpose is to

disseminate this knowledge. And also, if an opportunity should present itself, we would like to do some presentations in their professional conferences.

So now, in order, we can all do this. And this is a tentative time line. And because most of the time, we see each other at this meeting, so we utilize the upcoming -- several meetings set in our items there. So we hope the beginning the next year, we have the work plan.

And also, we started to -- between February and April, we have some recommendation language and have white paper in place, and so we can start to ask the Committee give feedbacks, and we can incorporate the modifications. In terms of report the dissemination, actually, we have started to kind of -- everything's, I think, working in the concurrent fashion; it's not a sequential fashion.

So, you know, like Sue already going to -- actually, this months' going to talk to AAPP.

And I had a chance to talk to Dr. Ostrander here too. And so we we'll use this kind of connection -- we can get things started.

So we hope by August, tentatively, we want to actually finish the project. And to finish the project, things including we -- what do we -- we don't have it down in terms of dissemination, activities, and all. So we want by that time submit the paper, because this one can reach all the people. And Bob and I already talk about what general to target it, and how we do that.

And also, I hope a year later, like November, if we will have additional activity reported. Also, by the time, we hope we know the manuscript has been accepted or not.

So I'm going to stop here and open for questions. And also, the other worker group members, if you have additional things, feel free to adding on.

DR. JOSEPH BOCCHINI: Thank you, Mei.

Debi.

MS. SARKAR: Mei, I was just going to remind you that there are organizational liaisons that are sitting here around the table, and you may want to work through them as well as through your Committee members.

DR. MEI BAKER: Yep. The Sue -- and you can working together on that. That'll be great.

DR. JOSEPH BOCCHINI: Okay. Other questions or comments?

(No audible response)

All right. Well, we'll --

DR. ROBERT OSTRANDER: Actually, I have --

DR. JOSEPH BOCCHINI: Yes. Robert.

DR. ROBERT OSTRANDER: Yeah. Bob Ostrander, American Academy of Family Physicians. I want to mention, I guess, just so that we're all aware, of what an uphill battle some of this is going to be, even though the concepts are not very difficult. In my efforts to promulgate some

of this as educational things in our journals, in our meetings, it's been a really hard sell because primary care physicians have limited continuing education time and so on and so forth.

And typically, when they go to meetings, they look for topics that are things that they're struggling with every single day that are a big challenge. And it's hard to get them to come to the -- no matter how interact it is -- to come to something on, you know, the nuts and bolts of newborn screening or how to deal with an abnormal result.

And I'm not saying we shouldn't do it. I think we're going to, and I'm trying to think of creative ways myself, as I bring this in, to include it. I think one of the things that I'm going to do -- and this is why I'm going to throw this out there, that you might find helpful with dissemination -- is link it to something that is likely to draw them into the room for the talk, and so they'll pick this up along with it.

So when it comes to this sort of thing, the challenge is that we -- at least in family medicine -- face every day, aren't newborn screening; it's the 23andMe question. It's the cancer genetics question. And people will come into a room to listen to a talk, or they'll read an article about cancer genetics and genomics. And you know, if you can make some of these presentation include newborn screening as a genetics session, you'll get people to come. If you just set it up as newborn screening, I think you're going to have a harder sell.

DR. JOSEPH BOCCHINI: Okay. Thank you.

All right. Mei, thank you very much. I look forward to this as it progresses.

So next on the agenda is new business. Is there any new business that Committee members would like to bring up?

(No audible response)

Hearing none. That ends our agenda, so that --

I want to thank everybody for their participation. I think we've had a really excellent meeting, and lots of broad participation. So I thank you all for your efforts prior to and organizing, those who worked to put their presentations together. I think we had a really excellent series of presentations.

So I thank Catharine. I want to thank the leadership at HRSA for having this so well organized.

And so there's no other business. We'll conclude the meeting. Thank you all very much. See you in February.

(Applause)

(Meeting concluded)