U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

HUMAN RESOURCES AND SERVICES ADMINISTRATION

DISCRETIONARY ADVISORY COMMITTEE ON
HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

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MEETING

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THURSDAY
SEPTEMBER 11, 2014

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Joseph Bocchini, Chairman, presiding.

PRESENT

JOSEPH BOCCHINI, Chairperson, MD
DON BAILEY, PhD, MEd
NATASHA BONHOMME
JEFFREY BOTKIN, MD, MPH
COLEEN BOYLE, PhD, MS
FREDERICK CHEN, MD, MPH, FAAFP
SIOBHAN DOLAN, MD, MPH
DENISE DOUGHERTY, PhD
CAROL GREENE, MD
DEBORAH GOLANT BADAWI, MD
COLEEN BOYLE, PhD, MS
CHARLES F. HOMER, MD, MPH,
KELLIE KELM, PhD
FRED LOREY, PhD *
DIETRICH MATERN, MD, PhD
STEPHEN McDONOUGH, MD
MICHAEL LU, MD, MPH
MELISSA PARISI, MD, PhD
NANCY ROSE, MD
DEBI SARKAR, MPH

SUSAN TANKSLEY, PhD
BETH TARINI, MD, MS, FAAP
ALEXIS THOMPSON, MD, MPH
CATE VOCKLEY, MS, CGC
MICHAEL WATSON, PhD, FACMG
CATHERINE WICKLUND, MS, CGC
ANDREA WILLIAMS

*via telephone

P-R-O-C-E-E-D-I-N-G-S

A. **Welcome and Roll Call**

Dr. Joseph Bocchini welcomed the Committee members and other participants to the fifth meeting of the Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC). Ms. Debi Sarkar, the Health Resources and Services Administration's (HRSA) Designated Federal Official (DFO), also greeted the participants and reviewed the rules concerning lobbying for Committee members.

Dr. Bocchini took the roll for the first day of the meeting.

Voting members present were: Dr. Bocchini, Dr. Don Bailey (afternoon only), Dr. Jeffrey Botkin, Dr. Coleen Boyle (Centers for Disease Control and Prevention), Dr. Denise Dougherty (Agency for Healthcare Research and Quality), Dr. Charles Homer, Dr. Kellie Kelm (Food and Drug Administration), Dr. Fred Lorey, Dr. Michael Lu (Health Resources and Services Administration), Dr. Dietrich Matern, Dr. Stephen McDonough, Dr. Melissa Parisi (National Institutes of Health), Ms. Catherine Wicklund, Dr. Alexis Thompson, Ms. Andrea Williams. DFO, Ms. Debi Sarkar was present.

Nonvoting organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Frederick Chen
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- American College of Obstetricians and Gynecologists (ACOG): Dr. Nancy Rose
- Association of Maternal and Child Health (AMCHP): Dr. Debbie Badawi

- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes (MOD): Dr. Siobhan Dolan
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

Approval of May 2014 Meeting Minutes

Dr. Bocchini indicated that a copy of the minutes for the May 2014 DACHDNC meeting was provided in the briefing book for this meeting. The Committee members in attendance unanimously approved the minutes.

I. Pilot Study Work Group Update

Dr. Jeffery Botkin updated the Committee on the goals, tasks, and planned activities of the Pilot Study Work Group. The group focuses on supporting current pilot studies and evaluation efforts. It is also responsible for identifying resources that could support pilot studies and evaluation, providing recommendations to the Secretary of Health and Human Services (HHS) in support of the DACHDNC condition nomination process, studying approaches to developing a network of states that could support the infrastructure needed to conduct pilot studies, and identifying information required to move a nominated condition to the evidence review process. The group will meet by conference call in October and anticipates conducting a panel presentation on relevant pilot studies during the next DACHDNC meeting.

II. The Inborn Errors of Metabolism Collaborative – Update

Dr. Susan Berry reported on the history and current activities of the Inborn Errors of Metabolism Collaborative (IBEMC), which is working on a long-term follow-up (LTFU) and treatment protocol. This effort began in the Region 4 Genetics Collaborative, with the review of treatment plans contributed by partners, identification of essential elements of LTFU, and initiation of data collection plans. The project evolved into an effort to develop a larger scale, web-based follow-up record, the Inborn Errors of Metabolism – Information System (IBEM-IS), as a platform for research that could serve as a model for a national platform.

The IBEC-IS initially focused on medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Initial steps included developing a demographic database and condition-specific data elements with the goal of developing data that was as uniform as possible. The project also defined issues for short-term follow-up and LTFU, developed processes for adding additional disorders, and developed processes for documenting consent to allow continuing contact and to engage subjects as participants in future research trials.

The IBEM-IS was initially funded in 2004 by HRSA through the Region 4 LTFU Work Group. Data entry into the IBEM-IS for MCAD began in 2007. Funding for the project continued from 2007 through 2011 through the HRSA-funded Region 4 Priority 2 Project LTFU. During this time, additional regional genetics collaboratives, including Heartland and the New York-Mid-Atlantic Consortium, joined the effort. Since 2011, the project has been partially funded through the National Institutes of Health Inborn Errors of Metabolism Collaborative (IBEMC). Beginning in 2013, the IBEM-IS included all inborn

errors of metabolism (IEMs) listed on the Recommended Uniform Screening Panel (RUSP).

The Newborn Screening Translational Research Network (NBSTRN) is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) through a contract with ACMG. It maintains, administers, and enhances resources to support projects related to newborn screening (NBS), particularly with regard to new technologies, new conditions, and new treatment and management approaches. NBSTRN has several research tools, including the Virtual Repository of Dried Blood Spots, the Longitudinal Pediatric Data Resource (LPDR), and the Region 4 Stork (R4S) tool. Most of the work described by Dr. Berry related to the LPDR.

(11:00 a.m.)

DR. BERRY: -- his work to develop some important research tools we're going to hear about R4S. I'm mostly taking view today in a little of the context of what ultimately came to be known as the LPDR, the Longitudinal Pediatric Data Resource, because we put our heads together with the folks at NBSTRN and developed data sets that now are the elements for these newborn screening disorder in the LPDR.

I'm also going to mention that work of the Joint Committee of the National

Coordinating Study and Follow-up Group and the Clinical Centers Workgroup who also -- I mean, I can't -- there are -- I wish I could name all of the people who gave of their time to create a consensus about what are the critical elements for a whole host of disorders.

That information and cooperative effort between those groups and our clinicians came together to form the LPDR and the data set we're now using. So our goals in our long-term collaborative project are to improve knowledge about the clinical history of persons with in-born errors of metabolism on a long-term basis and eventually to gather evidence about effective management and treatment strategies.

So we are a grant seed that has collaborated with tool generation for the LPDR with the NBSTRN. Is that enough alphabet for you? I can have more. I can do -- do you have a map with all the letters on them? Okay. But we are grateful to all of the people who brought this. This is a work of -- and they say it takes

a village -- it took like a giant city to do this, for which I am eternally grateful.

So what are our methods? Again, we've gathered elements for treatment protocols -- pretty much this is how the whole thing went. We also made the decision we, in our project, would collect this through prospective informed consent. That means, since we ascertain this at 20 visits with 3 meals, this is a sample of convenience. It depends on who says yes to the project.

Now we do not have a complete denominator, and that's an issue that will have to be addressed at some point. Nonetheless I think we have a valid and important data set. We gathered this in a Web-based, password protected way.

We did this originally through the organization DOC site and now we're fortunate enough to use the -- I don't know what else you'd call it -- I guess the CTA sponsored originally a suite of programs called REDCap or Research

Data Capture.

Okay, this is not intended to be read. It's intended to be impressive, okay. And what this is, of course, is a list of all of the primary core conditions that are metabolic that have been approved for the recommended uniform screening panel plus the secondary conditions. And we have data collection tools for all of these, even for things that people have never seen and may never see, as far as I can tell. But we can collect data about it if any of you ever get one of these cases.

All right, this is -- I kind of like this slide so I guess it's pretty. But this tells you a little bit about our growth over time. This doesn't go back to the origin of our thing because it would kind of go off the bottom, so I didn't put it in there.

But this is just to show a year-by-year account. And you can see we're pretty close to 1500 in January. These are

grouped by disorder. We didn't originally add PKU. For example, it was one of the later ones we put in because there were already data sets of people collecting.

But we ended up, after a lot of discussion, saying, well, that was nice but not everybody used those data sets. Not everybody had access to them. Not everybody was using -- it was primarily drug companies that were collecting information that they really wanted.

So people wanted a way to collect information about their PKU patients and so we added it and quickly PKU became our number one item in our data set. And we also have the big orange bars, MCAD, and not too surprisingly that's the one we have the most data about just about.

Again, this is not designed, necessarily, for you to read all of this. I'm just going to use this as an illustration. This kind of shows you about our collection by

disorder since we started REDCap entry. And it's disorder by disorder.

The reason I mainly showed this is to show you what the biggest bars are and kind of how they move. The tallest bar -- I don't know if I -- yes, I do have an arrow, that's good.

This tallest bar, of course, is a PKU and hyperphenylalaninemia or, as we now should refer to it, phenylalanine hydroxylasedeficiency. And we continue to have, I think, a, quite a substantial data set for that. We're approaching 500 cases.

This one is MCAD. Again, it was our first one so we have lots and lots of them. These two other ones, though, are pretty large as well. They're biotinidase and galactosemia. And there's a lot of interest in our group in those so we have a lot of them.

The next biggest one is the LCHAD. And that's really a pretty rare condition. We're coming up on 100 cases of that. I would

argue that's one of the largest -- the LCHAD, data sets that exist including most of it with genotype data because that's one of the critical elements for really being able to diagnose that disorder now.

Okay, so as of August 20th, when I presented this to my own group, we had almost 1700 subjects with demographics entered. They ranged in age from less than a month to 62 years, so some of these are pre-newborn screened folks, of course.

There were 289 individuals who were over the age of 18. They're average age was 11 years. And there were, not too surprisingly, about half and half -- slightly more males than females. We didn't have answers for race for everybody but, of the 1400 we did, it's predominantly white people.

And I don't know that that represents who says yes. I don't know if it represents the distribution in the states we're in. I'm guessing that we have a skewed

population of acceptance, but I don't know that for sure.

I apologize. I think these numbers may be rather small. So I'm just going to walk you through what's here rather than try and have you it read very much.

But I mentioned the idea that we asked people if they wished to be, you know, be part for -- available for recontact for research activities. And when you ask that explicitly about 80 percent say yes but 20 percent decline. And I think that's been -- that's another sort of reminiscence of the uptake of people when you ask them.

And things like Michigan where they have the consent to keep my spot kind of things -- that's a pretty uniform number and I don't know that we'll ever go tons over that. It's interesting because these are folks who already did consent to be in the data set. They just don't want you messing with them later.

The with regard to diagnosis

characteristics in our group -- by far the largest reason for diagnosis in this set is newborn screening, 82 percent. Some of them have multiple reasons. But if they have -- sometimes they have newborn screenings and a family member and some, a clinical finding but we still -- they are allowed to pick multiple answers for that.

Very few of them were just by lab abnormality, only about 1 percent. But there were about 11 in this data set that were clinical only.

Just as a representative kind of piece of information that we can gather we asked how many people had genetic counseling about their disorder. And, overwhelmingly, people do receive genetic counseling. We were really actually pretty excited about that.

And we thought a little bit about it and then we said, most of the people are at academic centers and they have counselors around. There may be good reasons for it but we think

it is essential, so we like to know that they have had it done.

I thought this is a slide that holds for this group specifically because I think you'll be interested in -- this is just taking numbers and making averages, okay. Don't relay a lot of information to it but I still thought it was interesting.

We had information about a little over 1,400 subjects in the data sets of whom a little over 1,000 were identified by newborn screening. And what we asked about was the time to intervention for their disorder after birth.

We had 771 in the whole data set that had that element specifically completed. When we averaged that number for all the disorders, and there's some real outliers in there, the average was 20.5 days.

You're going to hear a little bit more tomorrow about some work with regard to identifying critical conditions that need more

rapid responses so I split it into two groups -- those that were critical and those that weren't.

And I thought it pretty interesting that the time to intervention for the critical disorders was substantially shorter than that for the non-critical.

I think that makes total sense, but I thought it was an interesting confirmation of our intuitive sense of those disorders and I think it shows that we have the potential to gain continuing information about these issues through a data set like this. But that's just the very first pass at that question.

I'm going to tell you a little bit about one study that we've actually -- and I'm going to show you this information from our SIMD presentation -- I mean, our ACMG presentation which was a year ago.

And what we were trying to do with this is specific look at early complications of MCAD deficiency which is not too surprising

since that's the first thing we had data about. We wanted to assess the impact of the C8 value and to figure out whether genotypes had an impact on early complications.

So we abstracted some specific elements. We wanted to know, if they were deceased, the date of death. We want the mutation analysis if we had it. We wanted the C8 on the first newborn screening. We looked for lab abnormalities at the time that the child was first contacted. And we wanted symptoms at the time of the initial metabolic contact.

These are all multi-checkboxes so we know what they, kind of the symptoms are and where they are so we can sort them a little bit. And we wanted to know what the initial diagnosis, how the diagnosis was made because we really needed to sort for those that were newborn screened.

So at that time we had a little, almost 250 subjects with MCAD, 202 of whom were diagnosed by newborn screening. And none of

the children who had been diagnosed by newborn screening had died.

We had 17 subjects, just for comparison, who had been diagnosed by clinical presentation. The others may, I think were a family. We had 170 newborn screening subjects who had C8 values. At the time we did this their average age was actually about five years, and they were pretty evenly divided as males and females.

We had 147 of those with at least one allele and 124 of those had one of the common 985A>G. What I did, for simplicity of analysis and because it's really graphic is I took all the newborn screening values and put them on a graph. And then we divided them into quartiles, the lowest and second and third. And then what I did was compare the lowest and the highest ones.

And this is a representative of MCAD-related symptoms or laboratories summed up for individuals with MCAD deficiencies.

And it's pretty striking difference between -- the average number of MCAD-related labs is significantly higher than that in the low C8 group.

Similarly, the average number of MCAD-related symptoms in the high C8 group was significantly higher than that in the lower quarter. So this one looks at, we've said if you have -- how many 985 alleles did they have? Did they have no 985s? Did they have 985 plus another or were they homozygous with a common.

So it shows you that you don't have to have a high C8 to have two alleles or vice versa. But it also shows you that for the portion of patients with two 985 alleles it's significantly higher in the high C8 group than the low C8. And this was highly significant in the analysis.

All right. So we concluded that the higher C8 values found in any one screening were much more likely to be associated with lab

abnormality symptoms and homozygosity for the common allele.

We also found that the children with high C8 values are much more likely to have clinically concerning symptoms or lab values. This actually changed our practice in the area for most of us.

I think people originally, when they saw that we were screening for MCADs, thought the kids would get sick when they had first diarrheal illness and it is clearly emerging that that is not enough.

Children, particularly with the high C8 values, are probably stressed infants and are at significant risk for a neonatal as opposed to a six-month complication.

Okay, so where are we now and what happens next? We, through our collaboration with NBSTRN, we are now using the REDCap Web-based data collection. We have a separate -- instance is how it's technically described -- a collection of a suite of programs that is

found through MPHI. It mirrors directly the elements that are in the LPDR through NBSTRN.

We've added condition-specific research programs so that we can begin to analyze this data. We are continuing enrollment in data collection and we've been adding new participating centers. We've been doing collaboration with other research projects to serve as a data home for some of them.

We hope to be able to add specific research surveys that are to be -- because this is -- it should be used as a module essentially. You get demographics, condition-specific elements. You can also add a special research survey for Disorder X. And so it's very flexible in terms of collecting information.

We hope to be able to enable public health leaders to make informed decisions about their optimal investments in newborn screening. Folks, you can do it. And we're going to publish our initial findings from

these largest data sets.

We just had a large working meeting to define a set of I guess it was probably about six or eight papers that we think are feasible from our initial data sets. Just a reminder, this is our public Web site. We recommend that everybody go and see all the very cute pictures posted here. I'm hoping to put one of my own baby grandchild up there soon -- two days old. Oh, yeah. Thank you. She's really cute.

This is our center. We have 27 metabolic centers in 20 states. The ones with red are people sort of who have been processed working on IRB. The blue ones are the ones that have active data collection. The white ones are two people -- two centers -- that began data collection but needed to drop out. We still have their data but they're no longer collecting.

And this -- I wish this was bigger. I wish I could tell you each and every one of

these names. But this is a list of the actively gathering data groups. The ones with asterisks are NIH-funded centers, but all the rest are funded by regional collaboratives.

The purple is mountain states. The green ones are from NYMAC. The yellow ones are from Heartland. And the blue ones, from Region 4. So we continue to have collaboration with our HRSA-funded regional collaborative colleagues. It's a nice combination of work.

These are important people in our own group -- Cindy Cameron, my co-PI, Sally Hiner, our project coordinator. Kristi Bentler is out clinical consultant. She's the one who's hammered out the details of most of the data set with our project statistician, Shaohui Zhai.

MPHI staff, the usual fabulous acknowledgments that I like people to pay attention because these are really the only reason we're here. And so I don't usually make a fuss over them but it's really important to

realize how many things came together to enable us to do this.

And I think that's it. Thank you. I'm happy to answer any questions that anyone has.

CHAIR BOCCHINI: Sue, thank you very much. That was an excellent presentation and you provided us with some really nice data. This was really excellent, excellent work.

DR. BERRY: Coming along.

CHAIR BOCCHINI: All right, so we'll take any questions or comments, first from the Committee and then from the partners. Steve?

DR. MCDONOUGH: All right, Dr. Berry. Thank you for that excellent presentation. And, in your opinion, isn't 12 days intervention for a critical newborn metabolic condition too late in certain circumstances?

DR. BERRY: Okay, I should show -- I didn't go through all the caveats and details

about why that information was a little skitter-scattered. It only took two major outliers to make that data that long, that time that long.

And I didn't feel that, when I was just doing a rough pass and I don't have more information that I could legitimately take out the major outliers. But, literally, there were two patients that made that that long. I think the number, when I actually shook it down, was more like 5 days.

So I think -- you'll hear more about this when we talk about critical conditions, but there is no way that newborn screening is going to identify every child that's going to be symptomatic before they have -- get sick.

There are certain disorders that precipitate prior to the time that newborn screening can capture them. I still think it's important to screen for them but we'll never catch those kids unless we have some sort of bedside strategy.

With regard to the 12 days, yes, if 12 days was a real number for some of the critical conditions it would be after the barn door was completely off the barn, much less just closed. That's a long time.

CHAIR BOCCHINI: Jeff?

DR. BOTKIN: All right, Susan, thanks so much. This is really such important work, so congratulations.

DR. BERRY: Well, thank you.

DR. BOTKIN: Do I understand that kids who are enrolled have data collected with each of their clinic visits with the sub-specialists?

DR. BERRY: Yes. And I should be clearer about that because this is a bone of contention for a lot of folks. When we set it up originally we thought that one of the variables would be how often did people get seen.

And the best way to analyze that was to know exactly how many visits they had. And

the way we chose to do that was by having a relatively short interval visit summary each time. It's not a lot of questions but we collect data every time they come.

It means you have a lot of data points. That's not necessarily bad but it means collapsing the data some time will be tricky. It was a strategy choice we made. May or may not have been ideal but it's the way we chose to do it.

Others have chosen to do these things at intervals and then collect the number of visits. But it's harder to get granular information about what's happened time by time to the kids.

And we're doing things like how many hospitalizations did they have, how many emergency room visits did they have, did they have surgery, did they have anesthesia -- those things in between. And if you wait and try and collect that after six months, very hard to get it. Collect it each time they come, it's just

the information you get for their note.

And one of the things you want to do eventually for this, people, is you want to make this part of the work that you do when you see the patient in clinic. If you did it that way we'd have easy, facile way to collect the data and it would be quite informative, I believe.

DR. BOTKIN: And do you think there's opportunities for collecting data directly from parents?

DR. BERRY: I think there is. I think that's a very complementary way to do it. I think the problem isn't that numbers -- the information is slightly different. And I believe the emphasis and outcomes -- no, not the outcomes so much, but I think the emphasis with what parents want to collect and what the clinicians want to collect might be slightly different.

I think they're complementary and are synergistic, not opposing, data sets. I think they're really important to exploit from

both directions.

CHAIR BOCCHINI: Coleen?

DR. BOYLE: Well, Sue, it's just exciting, really exciting, to see the work that you have been doing and watching --

DR. BERRY: Thank you.

DR. BOYLE: -- and watch it develop over time. And I think your example around MCAD is just perfect in terms of thinking about how we can improve the clinical management of these children, so very, very exciting.

I was thinking a little bit about disparities, you know, thinking about this system and how it would be demo-lizable, you know, beyond the convenience sample that it is and then also thinking about disparities in care.

So I don't know if you've given any thought for that. I know you -- but in terms of how this convenience sample attracts that to all children identified. You know, you just talked about the racial and ethnic issues

around there. So it doesn't mean it's not a wonderful system.

DR. BERRY: No.

DR. BOYLE: It's clearly going to be improving quality of care but just thinking about how that attract that.

DR. BERRY: How can we get at that more effectively.

DR. BOYLE: Yes, the disparities related issues.

DR. BERRY: Well there's two issues here, I would say. One is it's a very complex and intense data set. There's a lot of information there. It's not realistic for every -- I don't know. It might not be realistic for everybody to do.

But I believe, and we've worked with others. There's strong work at the NCC to define a subset of these elements that would be maybe on the order of 30 to 35 that would give you long-term follow-up data, give you a good snapshot that could be collected on a more

population-based way.

And I think that that's going to be an important -- the trick is they fit in the same boxes. And if you can do something appropriate with being able to eventually link them you could say, take the newborn screening data, link it to this subset or little tiny -- it would sort of be a core set element.

And then you could open a conduit that would link those to the fuller data set for individuals that they chose to have it opened. I see this as all as linear boxes lining up. Whether that's right or not, I see it as the potential for that.

And that's sort of my desired vision. Whether that's true or not, I don't know. I think with regards to that I think you would certainly be able to get a more uniform, though more succinct data set for a common -- for a denominator.

And then the other question you asked was --

DR. BOYLE: No, I think that --

DR. BERRY: Is that answering what you want to know? Yes, I think we would be able to get at that. The question, the trick here is to use the same words and so the language is so -- I didn't know this when I started, but I learned a lot about language and how important it is.

And it's not just the words we say. It's how you identify something -- their addresses. It's like a long series of mailboxes, is really what it is. You have to have the right addresses.

CHAIR BOCCHINI: Dietrich?

DR. MATERN: Sue, this is great work. And I wonder, there are so many patient registries out there for lysosomal storage disorders. How do the data sets -- are they different and are there things that we can learn from each other?

And could those registries that are really hard to get to the data because they're

owned by specific groups or industry could be moved into what this is, hopefully a more transparent system?

DR. BERRY: So I'm going to -- little bit, put by NBSTRN hat on and look at Mike and make sure I don't say anything wrong about this. But the point that I would have is that there shouldn't, in my view, be any reason why we shouldn't be able to do something that we consolidate some of these under the guise of an honest broker, essentially.

The trick for incorporating data sets like that and then comparing them to others is mapping and it's, again, providing the right addresses. Should this intrinsically be possible? I think it should. Will it be possible? It kind of depends on whether the pharmaceutical companies want to be part of that effort.

Some of them are much more willing to do that than others, I would say. And the ones that are willing are going to be very

welcome under this umbrella. I think there could be a lot to be done to take that information and make it more generalizable, personally.

Is that a fair enough representation? NBSTRN can help facilitate that, I believe.

DR. WATSON: Suppose I can add. We're finishing all of the data sets on the LSDs.

DR. BERRY: Oh, lysosomal. You can tell them. You go ahead. That was a good one.

DR. WATSON: On the lysosomal disorders in about two weeks. There's a grantee now who was funded to do this kind of work for the LSDs that are part of screening. So we're going to be, we have about 90 percent done, 7 or 8 of the LSDs that are either in or candidates, near candidates for newborn screening.

And all that'll be up and running

around the time, hopefully around the time that NICHD announces who's going to get their contract to run a pilot for the LSDs.

DR. BERRY: And the idea is that we can use the common data set that was defined by the NCC, clinical center's workgroup that we've incorporated into our data sets and build -- use that as the foundation for the LCs because some of its just stuff that everybody wants to know.

CHAIR BOCCHINI: Don?

DR. BAILEY: Just a brief follow-up on Jeff's point about whether there could be a caregiver or a parent perspective incorporated in this kind of work. So I think, as a committee, we hear a lot from parents who really are advocating for their condition to be added to the roster or parents who are thankful for the work that the Committee has done.

But there's a whole large -- there's a very large group of families out there who have been identified through newborn screening. And, as you say, through the next

80 years they're living their lives and some of them are getting great services and some of them are not. And that's one of their major gaps there.

And I think we don't really have a good handle on that perspective because they get lost in the -- they go down to the specific caregivers and systems and so forth. And so I think, ultimately, some type of really more public health, services, research that follows up parents of kids identified through newborn screening longitudinally is really needed.

DR. BERRY: Our data set does contain elements that have items like that. We collect information about special needs, special education, referral for services, and distance to providers.

So we try to respect that in the data we collect but it would, indeed, be complementary to things that parents could do.

DR. BAILEY: Is that data provided by the parents themselves or is that data --

DR. BERRY: It's collected at the time that the parent comes. It's a question, are you getting enough school services, what kind of services are you getting. So it's a reflection of the parents' conversation with the clinician.

DR. BAILEY: Yes.

DR. BERRY: Not directly from the parents, but it's the -- and under our circumstances, the best we could respect that.

DR. BAILEY: Sure. Okay, that's great. Thanks.

DR. BERRY: Mm-hmm.

MALE PARTICIPANT 2: Thank you. Two questions -- first is kind of a process question. Just help me understand how your effort and LPDR work together and are not doing similar, too many different things.

DR. BERRY: Well so let us just say I think that our work with LPDR was the --

(Whereupon, the above-entitled matter went off the record at 11:38:14 a.m. and

resumed at 11:3:41 a.m. due to telephonic interference)

DR. BERRY: -- is the nidus or the core of the data sets. It's the starting point from which it can be built. And so that was why our collaboration with NBSTRN was like daily and fundamental for a while.

Christie Bentler, our clinical consultant, and Amy Brower and the tech people at BENCHOP and MPHI were all sitting on the phone hammering out the strategy for how those REDCap data sets should look based on our own original DOC side data sets, the data sets that we defined as critical elements from the NCC/NBSTRN joint workgroup.

And so we tried to bring all of that together in one grand gamisch. The LPDR, as it stands right now, we're using the tools we built with the LPDR. It's like a one-on-one correspondence. So it was a really intimate connection between those.

MALE PARTICIPANT 2: All right.

DR. BERRY: Yes, so we used the resources, I hope, efficiently and effectively.

MALE PARTICIPANT 2: The second question is actually a follow-up to Coleen's first one. I really appreciate you sharing the racial demographic data because we don't oftentimes get to see it. It is, however, concerning.

DR. BERRY: Yes, I agree.

MALE PARTICIPANT 2: That in a set of 1,400 folks there are only 11 Asian, 77 blacks it certainly suggests there's a bias somewhere. And if either there is bias in the newborn screening process itself, which should be population-based, or as you alluded to, somewhere in the recruitment there is real bias happening and into your data set.

And we need to be very thoughtful about what's happening here --

DR. BERRY: Yep.

MALE PARTICIPANT 2: -- and how to

correct that. This committee, we don't often get to see data at this level. And so when you do, it raises a lot of issues about sort of where we are in the science and what we know and what we don't know.

And if, in fact, it's about recruitment and potential bias there, that's something we can do something about and we really ought to.

DR. BERRY: Could I ask a favor and ask -- Kate, you collect data all the time. Do you see when you talk to families, that there are problems with this?

MS. VOCKLEY: Well, I think part of the thing we need to keep in mind is that we're not looking at any hemoglobinopathy patients in this data set. This is only inborn errors in metabolism. So that's part of --

DR. BERRY: But there shouldn't be a racial distribution for that either.

MS. VOCKLEY: But there shouldn't. And I'm thinking of our clinic population and

I'm actually not consenting the patients. I do the data abstraction. We --

DR. BERRY: In our own --

MS. VOCKLEY: I don't think there's a bias in who we identify --

DR. BERRY: Okay.

MS. VOCKLEY: -- obviously, as potential candidates for the database.

DR. BERRY: There may be a bias in who accepts.

MS. VOCKLEY: Well, and within the clinic setting they're given a list of patients who are candidates. And then it's up to the people who are in the clinic -- the nurses, the dieticians, whoever else -- to recruit, to actually talk to the patients about -- at least in our center that's the way it's done.

And there may be some bias at that point. That would be interesting to look at. And then there may be some bias, of course, in terms of who actually chooses to participate, perhaps for some of the historical reasons that

we've agreed to publicize.

DR. BERRY: Yes, I worry about that though.

MS. VOCKLEY: Exactly, mm-hmm.

CHAIR BOCCHINI: We're going to have to close this discussion. So, Carol, one last comment just so we can move on, Carol. And then one from the floor, and then that'll -- then we can move to the next discussion.

DR. GREENE: All right. And the discussion of bias is very interesting and clearly needs more explanation and exploration. I did note, I think that PKU and MCAD are the two diseases for which you have the most -- they're Caucasian disorders.

DR. BERRY: Yes.

DR. GREENE: So some bias comes with the diseases -- with the disorders. Asians should be reasonably common in PKU but you'd also have to look at the population of the states from which it came. So in the exploration just keep in mind the disorders.

DR. BERRY: All of those things are relevant. We still are very mindful of the fact that we want to make this accessible and useful for every child, so.

CHAIR BOCCHINI: So, for the recording, please state your name and any brief comment or question.

MS. SINGH: Yes. I'm Rani Singh, the profit director for the (indiscernible).

(Off-microphone comment)

DR. BERRY: Yes, it would be really important to compare what we reported versus what parents report.

CHAIR BOCCHINI: All right, thank you.

DR. BERRY: Thank you.

CHAIR BOCCHINI: And, again, Sue, thank you very much.

DR. BERRY: I really appreciated the chance to do it.

CHAIR BOCCHINI: It was really an excellent piece.

DR. BERRY: Thank you so much.

CHAIR BOCCHINI: Yes. Next, if all of our telecommunication issues are resolved, we have Piero Rinaldo on the line.

Dr. Rinaldo received his medical and research training at the University of Padua in Italy and then Yale University. Currently he serves as co-director of the Bio-chemical Genetics Laboratory and is Vice-Chair of Information Management in the Department of Laboratory Medicine and Pathology at the Mayo Clinic in Rochester, Minnesota.

Dr. Rinaldo is a professor of laboratory medicine and a T. Denny Sanford professor of pediatrics. He also holds joint appointments in the Department of Pediatrics and Adolescent Medicine and in the Department of Medical Genetics.

His clinical interests include the laboratory diagnosis of inborn error in metabolism, newborn screening, metabolic

disorders misdiagnosed either as child abuse or sudden and unexpected death.

To 2004 he has devoted his effort primarily the development and clinical validation of multi-variant pattern recognition software that improves the interpretation of complex profiles of laboratory results. So, Piero, if you can hear us, your first -- it looks like your first slide is coming --

DR. RINALDO: Yes, thank you, Dr. Bocchini. Can you hear me?

CHAIR BOCCHINI: Yes, we can. Great, so --

DR. RINALDO: And I can also advance the slides. Well, thank you for the opportunity. For me it's a little bit of a comeback as I served on the Committee for a while.

To tell you what we have done, it sounds like this is a Region 4 day but it's a nice segue way to the presentation by Dr. Berry.

And so the timeframe is similar. And we started again with the beginning of our regional collaboratives.

This is an outline of my presentation and I will try to keep it -- well, it will be a bit technical. But please try to keep it at a high altitude so we don't go too deep and --

MS. SARKAR: Dr. Rinaldo, I'm sorry. Could you please speak up a bit? We can't hear you that well.

DR. RINALDO: Okay, I'm using my phone and maybe I can put it closer. Can you hear me better now?

MS. SARKAR: That's better.

DR. RINALDO: Okay and I'll also try to shout. Sorry, so this is the outline of our presentation. And I will start again giving you a little bit of background about what Region 4 Stork that from now on I will describe also as R4S.

It all started with a HRSA really

driven regional collaboratives when there was a redistribution of resources and sort of the states were encouraged to work together. The name really comes from the fact that the states shown there, the seven states are, were labeled the Region 4.

And so this started as a quality improvement project. And we were able from the beginning to engage all seven of the states. Then in 2004 there was the selection of this project as one with priority. I believe it was priority one called the part of the regional genetics collaborative.

And we were funded for two cycles between 2004 and 2012. After the ending of the second cycle we made a very successful transition and R4S, the database, the infrastructure, is now part of NBSTRN. And you already heard from Dr. Berry extensively about it.

This is a slide that really talks a little bit about the evolution. We have 66

states and 235 programs. Now, when I say states, I really mean countries. In fact, as you can see, the smaller map of the United States, we have close to complete participation.

We have a total of about 1,130-some participants. So these are active users. Every year, the beginning of the year, we sort of look at people who have requested access and if they didn't contribute anything and also they never even accessed the site, we basically sort of inactivate the access. So this is a really accurate number.

The pictures you see there are from some of the face-to-face user meetings that we are being able to hold again with, because of HRSA support. And the very small pictures at the end are pictures of a training course that we have provided for seven years where five or six times a year anywhere between five and ten people are coming for a week-long training course.

We collect data. Like Dr. Berry, our data are in the form of laboratory results. There are 40,000 records, percentiles --- these are cumulative percentiles in every site. We also, again, trying to put it in perspective, we certainly are not Google. That probably is 10 seconds on Google, but so far we had close to 900,000 page views of our Web site.

What is really important is that we have being able now to collect more than 1.2 million data points of true cases -- so individual results of amino acids, acylcarnitine and related ratios from patients. Approximately 18,000 patients have been diagnosed by newborn screening.

And the last figure really is the most important because the main product, as you will see, of this project is what we call the post-analytical interpretive tools. These tools have been so far utilized 90 million times. Yesterday was a good day. They were utilized 179,000 times. Today we are already

up to 82,000. And, in general, the average is around 100,000 times a day.

Moving on, I think Dr. Berry earlier said that these pictures are not meant to be explained but just admired, so it's very colorful. But it's just an example of the type of output that we provide to users.

We, again, categorize things in two major groups -- what we call the productivity tools which is really a means to evaluate the evidence behind any condition, but also the comparison between different conditions and, of course, the post-analytical tools.

I have a series of slides that really try to compare what might have been sort of the standard and what we are being able to do in R4S. My experience, being involved with newborn screening now for about 15 years, that, certainly, before the collaborative, the regional collaborative, so at least my impression was that the collaboration was fairly limited.

We really have achieved what I can say credibly is a worldwide level of collaboration. And an example is really the author list of our first publication where we included no less than 247 co-authors from all over the world.

The second point is, again, trying to foster peer comparison. There has always been a lot of mystery and perhaps secrecy about the data. We were able to provide what we call the Comparison Tools where in our objective and confidential way we allow individual sites to see how their -- either referenced person totals or cut-off values compare to everybody else in the project.

So basically the idea is that you should see in this particular graph a lot of green squares in the middle, meaning that your cut-off is really matching very nicely compared to your peers.

We certainly have done a lot of work in trying to, I won't say change, but refine

some of the most basic definitions -- so what is normal. For us, normal is defined by combining all the data. You can see the concept of cumulative percentiles shown in the red ball.

We can tell that, A, (indiscernible) several million data points. The definition of normal, defined again as percentiles from the first to the 99th, is what is shown in the darker green. And then you can see where your own lab stands in comparison to the cumulative data but also comparing to all other labs that, of course, are not identified.

On the right side you can see the same thing as your cut-off value, if you use one, compares to other cut-off values and also to the disease ranges.

It is these ranges is actually, I would say, one of the most important concepts of this project because we are really revisiting the definition of what constitutes an abnormal result to initially, which is true,

not just for newborn screening but for anything done with numerical results in laboratory (indiscernible) it stays on, being above or below a certain cut-off value.

The definition is somewhat different because we're actually saying the definition of abnormal is related to when you start seeing evidence of what we call the disease range.

So those red boxes you see in the picture are the levels of different species, analyzed and ratios in VLCAD deficiency. And the blue arrows indicate that there is an overlap between the normal population, the green shade, and the disease range.

On the other hand, there are many other markers where there is a degree of overlap. And that is really the key point. So our process or intent to replace cut-off values in really driven by our emphasis on the recognition and the really ending of the portion of disease or reference ranges that do

overlap.

And we do this not by marker but by condition. So every condition in R4S can generate up to, up to this time, we called it the Plot by Condition, indeed, where you can see on a same, similar scale because everything is converted to multiple reference medium, how this analytics compare. But could be the same analytics that are abnormal in different diseases.

The other concept that certainly has been, I would say, an important contribution is that we have really moved away from a static, clinical validation. It means that you do it once and you are done.

The other is constancy evolving. The graph that you see there is showing the number of true-positive cases added per month or since January of 2009. The red dots just showing cumulative, you know, there are months with more cases, months with less. But on average we're adding five new cases every

single day.

Going back to the disease ranges, I already mentioned, so I just say it one more time, this is another example of Plot. We call it Plot and Marker for one particular acylcarnitine, the C14 species. And you can see that it's really different from disease to disease. And that's probably an obvious thing to say, but it really allows you to incorporate these differences not only in the recognition of a particular condition but more importantly in the differential diagnosis between multiple conditions that might have similar phenotypes.

We use a lot of ratios. In fact, this has, certainly has been a major theme as we try to educate users. I believe that, in general, ratios are grossly underutilized and that I hope -- I'll show you an example. It's something that should be addressed.

I use this example of three cases with one of a fatty oxidation disorders CPT-II deficiency. And you can see here, these are

the results of the primary markers. So when long chain species, from C14 to C18, plus some unsaturated species.

A true-positive case, compared to the medium cut-off -- that's the median for the R4S database, look like completely normal. A false-positive case actually has extremely elevated values, particularly what, in general is seeing those most relevant, significant marker, the species 316 is almost double the cut-off value.

This is a false-negative. It's an international case. It's not here from the United States where, again, that is also, say, and borderline to say the most. Now it's a completely different picture when we actually look at three ratios.

And these ratios are based and analyzed the old measure anyway. And, as you can see, that clearly the true, say, affected patients have a pattern that should not constitute a challenge to recognize. On the

other hand, the false-positive case looks perfectly normal.

The point is, as you can see, the last column has appeared. The right side shows how many labs actually do have a cut-off for that particular analyte. And it is really concerning to see that the three relations, they are far more informative, that the individual analytes are actually grossly underutilized.

This is another example of a Plot by Condition, again, related to CPT-II. And basically whatever is either on the far left or the far right are the most informative markers. And you can see that the clear ratios, either at the high end or the low end are, clearly, the one that can solve any difficult profile to be interpreted.

So my point is ratios consistently perform better than primary analytes yet, again, as I said earlier, are grossly underutilized.

Algorithms -- initially algorithms are sequential. You check something and there is only a yes or no or above or below a certain level. You move to the next level, you decide that something is normal. This is just a simple example of an algorithm based on the assessment of low citrulline for the detection of proximal urea cycle disorders. You measure citrulline and then a few ratios. And whenever you find a negative answer basically the screen is considered negative. If you meet all of those criteria the screen is considered positive.

And 4RS is a parallel algorithm. Everything is evaluated simultaneously in the context of a post-analytical tool. And that will actually give you a score that is either informative or not informative. That is what we describe as a parallel algorithm.

The differential diagnosis is also, going back to the early days of the work of the uniform panel, there was a lot of confusion and

often angst about the so-called secondary target where still some people believe there were unnecessary additions.

The reality is that we don't screen for conditions. We screen for markers. And most of these markers have a built-in differential diagnosis. And that's exactly what R4S can do.

They look over primary conditions, some of the secondary targets or things that are not perhaps on the radar of most laboratories. This is an example of a patient that just happened to have pyruvate carboxylase deficiency.

This is tool where studying the patient had a normal result for citrullinemia Type 1 or 2. And type 2, actually, was the most likely but also included pyruvate carboxylase. That prompted -- a person from that laboratory called me and said, what PC. And so we explained, well, it's a possibility. And it turned out the patient, indeed, had it.

So I will try to keep it very general. But, as I said earlier, the main part of this project -- of this collaborative project -- is what we call the post-analytical tools. And they're really driven by a quest for pinning clinical activity.

So we're looking for clinical, useful answers. And the questions can be yes or no. So we can ask a question, does a patient have a particular condition. That could be VLCAD, MCAD or citrullinemia Type 1.

We can also do, quite effectively, a differential diagnosis because two conditions. And then we can repeat the yes or no questions as many times as we want, basically, simultaneously.

This is just a graphical example, you know, an example of one condition. Two, the one that answers the question yes or no. It's not just about integrating more results in they single score. You might see there in the middle, on the bottom part on the left, that the

percentile rank. It's perhaps too difficult to see from there.

But this basically tells you where, compared to the existing evidence, in this case of 248 cases, where this patient would stand if, indeed, has VLDCAD deficiency. Obviously a case that the 95th percentile is a no-brainer. You don't need a tool for that.

You're certainly need tools to do a differential diagnosis. The tool that has been most popular is the one that allows the differential diagnosis whenever possible, of course, between VLCAD and heterozygote patients.

This is the tool that, again, answers the question A or B or one or another. And recently were very pleased to see that the consortium of the Western state, by which their experience, a project led by Dr. Lawrence Merritt (phonetic).

And there is a particular this study I see our highlighted it here -- that we

actually look it their experience. We were at 27 cases that were confirmed by genotyping to be carriers. And this tool, without correctly predicted 23. So I consider these false-positives. So I said a tool that allows you to eliminate 23 out of 27 false positive is something that is clinically useful.

And finally, the All Condition Tool, that's what I already told you, is basically ask a question, yes or no, simultaneously show all conditions using condition-specific disease ranges and no cut-offs. So that's one or more sometimes out of the group.

The question, of course, is does all of this make any difference. And there are certainly now, there is evidence emerging from other programs. But I can tell you what has been our program.

While the detection rate has remained fairly stable, below 1 in 2,000 births, this slide shows the false-positive

rate that we experienced in Minnesota between 2001, actually, and 2013. The period of 2004-2014 is when, actually, the testing was performed in our laboratory at the Mayo Clinic.

So in that period, and we focused on the last year, 2013, there 71,000 babies. And we reported out only 55 cases. 38 were real, 17 were false-positives. We do not report out TPNs and never ask for a repeat sample.

That tabulating a false-positive rate of 0.24 percent and a positive predictive value just shy of 70 percent. Based on the data we had we had in our fourth we can say that the average false-positive rate out of 28 program is 0.51.

So we use this data, actually, to come up with, I would say, more practical metric. And that's what we call the false-positives per week. And you can see that, in Minnesota, we had a little more than one per month when on, average, in the United States, it's one per day.

So that brings up to what we can do if, you know, for us, beyond tandem mass spectrometry. And for this presentation they came up with the double 100. And I will explain what that vision is -- or maybe it was a dream.

There is also a quote there will be other tests that will be as important. That actually is a gem that I obtained from Harry Hannon that years ago sent me this quote from a presentation that Bob Guthrie himself made in 1979.

And he was actually reminding his colleagues that while there was a lot of emphasis on screening for congenital hypothyroidism, he said there are other things that can be tested, and there will be other tests that will be as important. I think, I found it beautiful.

So let's put it in perspective. The uniform panel, unless your committee just changed something very recently, I believe its 57 conditions. But if we look at what is a

partial list of candidate conditions that these things I've heard have been or are under -- might be soon -- under consideration.

Even if we take all of those as individual and count them as one we will go off to 74. And, of course, if you're standardizing lysomal storage diseases you can get up to 87.

Or it you expand the paroxysmal disorders or you expand the creatine disorders, basically you end up quickly to a situation where you are dealing with probably more than 100 conditions that might not be added to the panel but certainly might actually come across the table of your committee for discussion about it they should or should not be included.

And this, of course, means that if there is a primary condition, they will be secondary targets. How can we possibly do that? Well I think multiplexing might be a compelling necessity.

So in other words the idea is to have a piecemeal addition, one condition at a time,

one condition, one test. I might simply not be feasible in terms of the manual resources.

I think that one of the lessons the learned is there will be a need to have evidence of much greater, stronger analytical robustness and reproducibility. In other words, learning as you go might really not be an option.

And, at the same time, because of the important work done by your committee and the evidence of your process, there will be a need to provide in-depth clinical validation. And this is sort of my personal favorite as I really have become really adamant about the importance, is we have to do better when it comes to performance.

And so performance must exceed by a lot what have been acceptable historical standards. We were between 0.1 and 0.5 per condition. Let me put it in a practical context.

These are fairly outdated data but it's the only one, or at least it's the most

recent I have which shows what was the experience in the state of Minnesota for the entire panel -- the metabolic disorders tested by MS/MS and then all the other conditions tested by the Minnesota Department of Health.

You can see overall there was close to 0.9 percent false-positive rate. That goes on my favorite metric. Let's say, okay, 0.05, 0.11 -- I'm not sure what it means, but I can understand a count or for an average number of false-positives per week. And in Minnesota it would have been 12 for everything.

Now we have 71,000 babies. California, obviously, it's just growing in a linear mode there will be, at the same level of performance that would be 95 false-positives per week. And if we look at the entire country it would be more than 700. And those are the numbers there.

So the reality that our performance, when it comes about MS/MS, certainly was a bit of an anomaly. In fact, if I bring back the

value that I showed earlier, the average out of 28 states, their programs, that shared there performance work metrics; it would be fairly different story if we plug in a 0.05 percent false-positive rate.

Because at that point, sorry, at that point you can see the numbers at the bottom, start going in a quite significant way.

So here is sort of the vision or the dream, if you want. Say what if you were able to push every condition to have a false-positive rate of 0.01 or less. So some conditions are already there, like biotinidase and galactosemia, or hemoglobinopathies. And in this slide also are the SCID.

But if we put all together and we say we must achieve that threshold then the numbers will actually decline. And, in fact that's how the 100 concept came up. I said if we look at this we can say that in another state like Minnesota there should be one false-positive per day. In a big state like California there

should be 10 or less. And nationwide we should have 100 or less.

So, again, in a very humble and respectful way, I'm just saying and suggesting to this committee that one factor to consider for the future evolution of a recommended panel would be, again, that, yes, we should actually add more conditions. But also draw a line that should be no more than 100 false-positives per day in the United States for all tests combined.

It is an achievable goal in my opinion. I'd really fixated on the false-positives. But we all have seen the recalls, the repeat analyses. I've seen cases being tested six times. There is a significant element of disruption of care, especially when you come to premature babies or sick newborns in the NICU.

There are these unnecessary visits to the emergency room. There are even admissions. Confirmatory testing, that could be fairly expensive. That could be a referral

to multiple specialists. That could be second opinion. More importantly, really looking at side of the patients.

This phone call, I mean, Dr. Berry was talking about this beautiful granddaughter and here you have these new parents, on top of the world and, boom, you got the phone call from a stranger that starts putting some doubt in your mind that something could be wrong with your child.

I really think we grossly underestimate the negative impact of this, not just from their feelings and their perception of their family but also, I mean, practically, on their work schedule. They might have to take time out of work, and that really affects the extended family. Everybody is stressed out by this possibility something might be wrong with the baby.

So, again, and this is just my opinion, so you can absolutely feel free to ignore it. But I believe that in the current,

particular future healthcare climate a national false-positive is an absolute requirement entitled to any extension of recommended panels.

How can we improve performance? Well, we can adopt, like some European countries have done, top screening. You might be able to appreciate values of pioneering the first evidence of the expression throwing the baby with the bath water from German in 1512.

Some people set their cut-offs so high that if I exceed that level it must be a true-positive. Some states have chosen to increase the frequency of testing. And that's certainly something you need to be evaluated. But also should be scrutinized -- is that really absolutely necessary.

I believe in your agenda you have vote about succinylacetone for Tyrosinemia type 1. It seems to me that certainly has proven itself as a reliable marker for that condition.

We try to prove our cut off values

and do our clinical validation or do more with what is being done already. What do I mean by that? Well, this is a paper that is in press and everybody's already in PubMed where we actually did an experiment with our colleagues in the department of Public Health in California where we actually took the data over a six-month period and we used those for some exclusion criteria, like we eliminate preemie babies or less than 24-hour specimens. And we said, okay, let's compare the actual outcome that was based on cut-off values and what would happen if we used the R4S2s? And this was applied to more than 175,000 babies. I just gave you the punchline. First of all true-positive cases in that cohort were correctly identified. Actually 1 of 2 false -- okay, I'm getting. I'm trying -- I'm seeing you now. Tell when I have to stop, but I'll try to go faster. We detected one or two false-positives.

CHAIR BOCCHINI: Piero, we don't

mean to cut you off, not to use the lab term cut-off level, but we have exceeded the time. And so if you could wrap up within the next five minutes we really would appreciate that. Thank you.

DR. RINALDO: That will be a bit difficult. But, okay, maybe we'll just skip the last part of the presentation.

CHAIR BOCCHINI: Okay.

DR. RINALDO: So here -- and I believe you have this as a handout. Again, by just using the tool the false-positive rate could have been reduced from 0.26 percent to 0.09. If all the other possibilities were adopted it would have gone down to 0.02.

If we plug in that 0.02 you can see that would have dramatically decreased the number of false-positive cases nationwide, creating room for more conditions. I guess probably it makes sense that I stop here because, again, I wanted to tell you what would have happened where adding more -- or act least

I believe it's more of your current discussion.

But, again, I'll stop here, especially if people want to ask any question. And I believe you have a handout, at least the one I sent to Debi.

CHAIR BOCCHINI: We do, Piero. I want to thank you. This was an excellent presentation and, again, another example of advancing information by collaboration and really working to consider how to better utilize the data. So we thank for that.

And the rest of your presentation -- we will invite you back to do the rest of the presentation. So we'll do it another time. So we won't lose it. So thank you. Let's open this presentation for discussion/questions. First one from the Committee. Charles?

Dr. HOMER: This is Charlie Homer. So it sounds as though all of the states or 48 of the 50 states are participating in your program. So what's the -- is it simply that

they're submitting data but not using the algorithms that you're providing?

Because otherwise you would think they would, if you're providing that information you'd think we would be able to be at that lower false-negative rate already.

DR. RINALDO: I believe many U.S. programs are using it. I'm not privy of their performance measures. We have a place on the Web site to post them but that is information that is somewhat -- seems to be users are reluctant to share, and I respect that.

Again, I believe that there are other independent reports of an improvement in performance after utilizing the tools. I believe Georgia may have some data soon and will present next month at the APHL meeting. But Sweden, some laboratories in Italy, and these are the ones I know of.

So when we look at before and after, consistently, we are seeing some times a sizable improvement.

CHAIR BOCCHINI: Thank you. Any other questions from the Committee or organization representatives? Yes.

MALE PARTICIPANT 2: Piero, is there a relationship between this effort that you're making and the CDC's efforts for laboratory performance?

DR. RINALDO: I'm not sure are are referring about the proficiency testing?

MALE PARTICIPANT 2: I think so.

DR. RINALDO: Oh, proficiency testing is really a point in time. So when a specimen is provided to the laboratories -- and I would say it's more a measurement of accuracy and precision, has been for quite some time.

Although recently the UDOT program was actually just doing what I think a proficiency testing program should do -- send your specimens and tell me if you find anything.

Before it was more measure these analytes and see how close you are to the expected value of what the analytes are doing.

So they are dealing with more of a QA/QC aspect and the absolutely necessary proficiency testing and documentation of. We are more providing really tools for everyday work.

CHAIR BOCCHINI: Other questions, comments? If not, Piero, thank you very much. We appreciate the presentation and being able to do this from a distance. That's, it was quite well done, so thank you. And we will invite you back for further discussion on the rest of your presentation.

DR. RINALDO: Okay. Have a nice day. Bye.

CHAIR BOCCHINI: All right, next on the agenda we have public comments. One person will be calling in. We have four individuals who are here. And so we'll start with Sarah Wilkerson from Save Babies Through Screening Foundation. She is on the line. Operator, can you unmute her line?

OPERATOR: She has been joined into the conference with an open line.

MS. WILKERSON: Great. Can you hear me okay?

CHAIR BOCCHINI: You'll have to speak up a little more. We can hear you, but barely.

MS. WILKERSON: Okay, is that better?

CHAIR BOCCHINI: That's better.

MS. WILKERSON: Okay, great. Hello, I'm Sarah Wilkerson. I'm a mother and a member of the Board of Save Babies Through Screening Foundation.

My son, Noah, passed away from undiagnosed MCAD, at a few days old in 2009. His story was featured in the article series done by the Milwaukee Journal Sentinel. Due to the state lab in Colorado where we lived being closed over the weekend, which delayed his test results until it was too late.

First of all, I appreciate having the opportunity to speak via the webinar access from home. I'm now too pregnant to travel with

a baby girl that's due in November.

I've spoken at previous meetings and would like to thank the Committee and especially the Laboratory Standards and Procedures subcommittee for the hard work being done to research the issue of timeliness with newborn screening.

It literally means life or death to babies, like my son, who exhibit problems early on with their disorders. I have a few questions. One is that part of the original plan was to reach out to the Joint Commission to see if guidelines could be added around timeliness.

There weren't any updates from this last time and I know that the American College of Medical Genetics had started it and was going to work with the committee to complete the task of approaching them. And I just wanted to know if this plan was still in place and what updates there might be.

Also, reaching out to the Joint

Commission would only impact hospitals whereas state labs share the responsibility of turning around test results in a timely fashion as well. And I wanted to know what reciprocal steps could be made to make sure that labs follow the same basic guidelines to turn around test results on time.

Along this line of creating a level of accountability with both labs and hospitals, I brought the idea to several members of the group last time to consider taking over the database created by the Milwaukee Journal Sentinel that tracks performance measures with timeliness of hospitals.

Perhaps the CDC or the APHL would be willing to take it over. You guys would know best where it should belong. But my hope is that by encouraging states and hospitals to stick to the best practice guidelines that the Committee has worked so had to create.

And also it would provide a roadmap of which labs and hospitals need to follow-up

in training to meet basic guidelines. And I hope the Committee is open to this idea.

I'd like to (indiscernible) of another family from my home state of Colorado. Just a week ago this family found that their child had come up positive for Cartinine uptake deficiency.

Their child was eight days old. And it was a disorder their pediatrician knew nothing about in terms of treatment. After reaching out to the Save Babies Through Screening Foundation to learn more, they were encouraged to take their child to the emergency immediately due to the nature of the deficiency and the symptoms she was already beginning to exhibit.

Thanks to the advocate's quick thinking with advising these parents, their daughter is fine with no long-term effects -- but eight days.

These parents are looking at the system and asking themselves the same question

that I asked myself when my son was born, that this is a life or death serious piece of information to have, and why did it take so long to find out.

So far, after some investigating of this particular case, it appeared the batching at the hospital level might have been the cause. So, as you can see, these sorts of inefficiencies are still happening and must be corrected.

I look forward to following the continued discussion on this topic, and I'm eager to help where I can. Again, thanks so much for your hard work. I really appreciate the direction that this project is going. So thank you so much.

CHAIR BOCCHINI: Ms. Wilkerson, thank you for your advocacy and your efforts. We appreciate them. As you know, on the agenda tomorrow, there will be a presentation from the Committee -- subcommittee -- a discussion and perhaps development of specific

recommendations.

So we appreciate your involvement and there will be more information for you available tomorrow.

MS. WILKERSON: Great, thank you so much.

CHAIR BOCCHINI: You're welcome. Next, if we could come to one of the microphones, the next I have -- the order is Steve Barsh, Lisa Seeger, Ann Moser and Annie Kelly. So if Steve Barsh could come. Oh, sure.

I just didn't if that worried you or not because have the next three people.

CHAIR BOCCHINI: Okay, so if you'll come to the microphone.

DEBI SARKAR: Podium.

CHAIR BOCCHINI: Oh, that podium is best. So great. So if you'll state your name and affiliation?

MS. MOSER: My name is Anne Moser. I'm from the Kennedy Krieger Institute in Baltimore. Thank you to the Committee members

and participants and attendees for allowing me to speak on newborn screening for x-linked adrenoleukodystrophy.

My late husband, Dr. Hugo Moser, and I began our research on x-linked adrenoleukodystrophy in the late 1970s at the Kreiger Institute in Baltimore.

It was Hugo's dream to identify ALD boys early by establishing universal newborn screening for ALD. Development of ALD newborn screening was a group effort, thanks to Walter Hubbard – at Johns Hopkins, Silvia Tortorelli at Mayo Clinic, Gerald Raymond, pediatric neurologist at Kennedy Krieger and now in Minnesota, our CDC colleagues for establishing some standards and to all the ALD participants, parents and the funding agencies.

The Standard of Care is well-established for ALD. One of the most important and available life-saving therapies for ALD is hormone replacement therapy for those ALD patients with Addison's disease.

Since the early 1990s bone marrow transplantation was shown to be effective in halting the central nervous system demyelination. It's done at the first signs of progressive brain dysfunction.

By 2010 several hundred ALD boys identified early by family screening have benefitted from bone marrow and umbilical cord cell transplantation as well as treatment for their Addison's disease.

The ALD screening technology on newborn blood spots works. The Mayo Clinic labs combined high throughput screening availability with five lysosomal disorders in a pilot study of 100,000 anonymous newborn blood spots.

And as of January 2014 the New York State newborn screening lab combined the high throughput screening of ALD with Krabbe's disease.

Both the Mayo and the New York Screening Labs use a second tier test -- the two

minute LC Column MS/MS assay of the c26 lyso-phosphatidyl choline developed in our Kennedy Krieger laboratory and at Johns Hopkins to eliminate all the ALD false-positives.

There were no positives in our published study of 5,000 newborns screened in Maryland. Thus, we believe that using the Column procedure as a second-tier test, the false-positive rate will be very low.

Mayo has confirmed 4 ALD positives in the 100,000 screened. And since January of 2014 there have been 160,000 newborns screened in New York with 6 ALD boys and 2 female carriers identified and confirmed by ALD gene mutation analysis.

Thus, the number of ALD babies detected by newborn screening is approaching the 1 in 15,000 incident rate predicted by family screening. New York state has established a follow-up network of referrals to pediatricians, geneticists, endocrinologists and pediatric neurologists.

We have heard from several of the newly diagnosed ALD families in New York that they are receiving appropriate support. And several of these families have made their way to the specialized ALD clinics around the country, namely at the Kennedy Krieger Institute and the one at Mass General and the one at Minnesota.

Today, on behalf of all physicians caring for individuals with ALD, the ALD researchers thinking new therapies for ALD, the ALD family support groups who have donated funds and are lobbying for ALD newborn screening and the many ALD families worldwide, we request that ALD be added to the uniform panel of screening tests performed on all newborns.

Thank you for your time and consideration of this important life-saving request to add ALD to the recommended list of disorders on the newborn screening panel. And I'm available for further questions if you have them.

CHAIR BOCCHINI: Great. Thank you so much. We appreciate all the work that you've done in this area and your presentation. Thank you. Yes.

MR. BARSH: Hello. My name is Steve Barsh and I'm one of the founders of the Stop ALD Foundation, a medical research foundation dedicated to the treatment and early identification of ALD babies by newborn screening.

Thank you for allowing to speak today and the continued time consideration you give this very important matter.

The Stop ALD Foundation appreciates that at the January 14 meetings the Committee voted to move the ALD nomination forward to external expert review. However, we cannot help but to be disappointed that eight months later your review has not yet begun.

We understand that there were several organizational items to be resolved including a rework of the public health

assessment. However, much can be done prior to agreeing on a new public health assessment approach.

We are encouraged to hear that the review will begin shortly and parallel with the review of Pompeii's disease. However, we urge implementation of more specific timelines. My emphasis on driving this process forward is not without cause. Today, every 48 hours, another baby is born in the U.S. with ALD.

This newborn screening test that works, as Ann referenced, a process, and follow-up and in the place that works that Ann just mentioned and corrective medical action that can save these children's lives and the enormous financial costs of treating children who are not screened and/or diagnosed too late.

Between now and when you go home tomorrow another child will be born in the U.S. with ALD. In the absence of screening the diagnosis will be missed and that child will be doomed.

As many of you I'm sure well know, the trend is for personalized medicine. In our family we had that experience. But I don't think this is what was meant. We had a personal screen in our family -- excuse me -- and his name was Oliver Laben (phonetic). He was my nephew. Excuse me.

Because of Oliver's post-symptomatic ALD diagnosis our family underwent genetic testing which revealed the presence of ALD in our son, Spencer Barsh, then just 11 months old. Spencer benefitted from the early warning, but it was one which came with the cost of a human life, his cousin, who was not diagnosed in time, before the brain disease occurred and who passed away.

With these early warnings Spencer was able to benefit from a cord blood transplant at Duke. And today he is a normal, healthy 14-year-old high school student who won top honors last year for not only math but science and swims on his school swim team. No special

services, no special needs, just a regular old ninth grader.

Well, he's a teenager, but besides that he's regular. Oh, and we both take mixed martial arts where he kicks my rear end. He's strong, healthy, smart and will make enormous contributions to society. He's living a full and active life denied to his cousin.

The ALD newborn screening test and follow-up process works and costs much less than caring for the children who are not diagnosed at birth. There were remarks earlier about false-positives. I think Ann's Davis shows there haven't been as many false-positives as are being done in New York which is extremely impressive.

The fate of these children is in your hands. Please do the right thing and do it quickly. Thank you for your prompt attention in finally getting this implemented. Thank you.

CHAIR BOCCHINI: Thank you, Mr.

Barsh. We appreciate your comments and your sharing of your personal story as well.

MS. SEEGER: Hi. My name is Elisa Seeger and I'm the president of the Aidan Jack Seeger Foundation. On March 29, 2013 New York State signed Aidan's Law in honor of my son who lost his life to ALD in 2012. And this is a picture of him.

In just eight months we have identified eight babies, six boys and two girls, giving these children and their families the information necessary to save their lives. While we have identified eight babies to date the reach is much further than that.

As ALD is an inherited genetic disease siblings and other family members can also be tested. I had the honor to meet two of the families diagnosed through newborn screenings. One of the families has a son who is four-and-half years old and, yes, he tested positive for ALD.

Luckily for this family, their

four-and-a-half-year-old son is still asymptomatic. And this is a picture of the two newborns and then the four-and-a-half-year-old. So proof right here that the newborn screening is working.

Ninety percent of the boys with ALD will also have adrenal insufficiency which, left untreated, can result in death. Adrenal insufficiency can present itself within the first six months of life. For this reason alone, ALD should be added to the recommended uniform screening panel.

This is a picture of Joshua who died at the age of two. And after four years of research this family found out that they son, Joshua, had ALD but died from an adrenal crisis which could have easily been treated with a simple pill that costs pennies a day.

How many boys have died from an adrenal crisis that was labeled unspecified but was in actuality ALD? A number that is too high and a number we will truly never have an answer

to.

The next points are a summary of what we know about ALD today. An estimated 235 babies will be born each year in the United States alone. We know that the ALD newborn screening test has proven to be accurate. We have eight diagnosed babies in New York state with no false-positives and we're up to about 185,000 screens.

The cost to add ALD to each state's newborn screening panel is minimal compared to the cost of caring for a symptomatic child. We know that early diagnosis is the key. Without the crucial early diagnosis these boys will die from adrenal insufficiency or ALD.

Medical institutions from all over the country have supplied letters in support of ALD newborn screening. The experts in ALD from the University of Minnesota, Mass General, Duke University, Stanford, Cornell, Montefiore, Johns-Hopkins and, of course, Kennedy Krieger, to name just a few, all concur this is the most

effective method in battling ALD.

Studies have concluded treatment prior to being symptomatic is the key to a successful outcome, stopping the disease and the ability for these boys to have a normal, healthy life. Cost-effectiveness of treating pre-symptomatic boys as opposed to symptomatic boys is astounding.

Pre-symptomatic boys can go on to lead a normal, healthy life as Spencer -- as Spencer did, while disease progression in symptomatic boys leads to an outcome in which these boys will need a high level of care for the rest of their lives.

Protocols are in place. Once a baby is diagnosed with ALD these can be used in every state. The impact on the health department if nothing is done is much greater if ALD newborn screening is not implemented in each state.

The countless amount of testing to get to the diagnosis as well as the level of care needed is and will continue to be an enormous

burden.

Finally, all of you sitting here today have the power to add ALD to the recommended uniform screening panel -- quickly. Please look at all the facts presented here today and make the decision to add ALD.

Please give all the future boys born with ALD the chance that Aidan and so many others did not have -- the right to a normal, healthy life.

CHAIR BOCCHINI: Ms. Seeger, thank you for your presentation and updating us on the New York data. And we really appreciate your coming here. Thank you.

MS. KENNEDY: After listening to these presentations, there is no question that the work you do is extraordinary, so thank you for what you do and thank you for allowing me to speak this morning.

My name is Annie Kennedy and I serve as the Senior Vice President for Legislation and Public Policy for the Parent Project Muscular

Dystrophy.

This morning I am here on behalf of the estimated 8,000 boys and men living with Duchenne muscular dystrophy in the U.S. today and, more importantly, for the thousands of babies yet to be born with Duchenne muscular dystrophy.

As many of you know, Duchenne muscular dystrophy is the most common fatal genetic disorder diagnosed in childhood, affecting approximately 1 in every 5,000 live male births.

Because Duchenne is found on the X chromosome it affects primarily males but occurs across all races and cultures. Young men with Duchenne typically live into their late 20s.

This committee is not naive to the devastating impact that a diagnosis of Duchenne muscular dystrophy has on a child and his family.

In addition to the fact that this

committee's membership includes some of the world's most esteemed advocates and clinicians in this arena you also heard from Dr. Jerry Mendel from Nationwide Children's Hospital and the Ohio State University in January of 2013 about the state of Duchenne and the rapidly changing diagnostics research and clinical landscape in this disease arena.

While Duchenne muscular dystrophy is still a 100 percent fatal disease we have demonstrated that immediate identification and early clinical interventions can add years, even decades, to an individual's life span.

Dr. Mendel's presentation provided a recap of the Duchenne newborn screening pilot he and his team have lead in the state of Ohio. Within the state of Ohio and funded by CDC Dr. Mendel and his partners led an extraordinary effort which included the state's 43 birthing hospitals, screening more than 40,000 babies during the pilot and identified 7 male babies confirmed to have Duchenne.

Since the Ohio pilot began the DNA mutation analysis has been even further streamlined and refined by work at Emory University. In the last year our landscape has changed and advanced even further, which is particularly why I'm here today.

In August, the European Commission granted conditional marketing authorization for PTC Therapeutic Translarna, known as Atalurn in the United States, produced in the European Union for the treatment of nonsense mutation Duchenne muscular dystrophy in ambulatory patients aged five years and older.

It is estimated that a nonsense mutation is the cause of Duchenne in approximately about 13 percent of patients which would be about 2,000 patients in the U.S. and 2,500 in the EU.

This fall, later this month, confirmatory trials for another promising therapeutic intervention will begin for Exon skipping led by Sarepta therapeutics in the

United States with an anticipated accelerated approval pathway slated for review of this therapy which could benefit another 13 percent of the Duchenne population whose disease may be modified through skipping of the targeted Exon 51 which would be an additional potential 2,000 boys in the U.S. who could benefit from that therapy.

In other words, this is the dawning of a new day in Duchenne muscular dystrophy, one in which we have a robust and quickly advancing therapeutic pipeline with recent conditional approval in Europe and cautious optimism for approval in the U.S. in 2015.

In each instance these therapeutic interventions will be most successful the earlier they are administered, meaning pre-symptomatic identification of children with Duchenne as early as possible is critical.

We also have a reliable validate diagnostic tool that has been implemented through a newborn screening pilot within the

state of Ohio which included a comprehensive outreach and support system for families being referred for screening and diagnosis.

And last, but most importantly, we know that providing clinical interventions to children with Duchenne before they develop muscle weakness improves therapeutic outcomes and can even add years and decades to their life span.

The Duchenne community is hopeful. We are a well-organized national infrastructure that is well positioned to move a newborn screening initiative forward. And we stand ready to work with your committee and other partners in this space in any way possible as we work towards our shared goals of optimizing health outcomes in children with Duchenne muscular dystrophy.

Thank you for your time today for all of your work. PPMD and our Duchenne community look forward to engaging with you as we work to make Duchenne newborn screening a reality.

Thank you.

(Whereupon, the meeting in the above-entitled matter was concluded at 1:46 p.m.)

CHAIR BOCCHINI: Thank you very much for your presentation. Thanks for updating the committee, and we certainly look forward to working with you in the future to bring forward a nomination. Thank you.

With that, that will conclude the public comments. What we've decided to do since we are somewhat schedule is to have lunch.

So instead of just having a break, we'll have an early lunch, but we want everybody back by 12:45 so that we will then move the last presentation of the morning session into the first part of the afternoon.

Okay. So we will adjourn now for lunch, and please be back promptly at 12:45. Thank you.

(Whereupon, the above-entitled matter went off the record at 1:47 p.m. and

resumed at 1:51 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

CHAIR BOCCHINI: All right, let's go ahead and call the afternoon session to order. Welcome back to the afternoon session. We're going to start by taking roll. I'll start with myself.

(Roll call)

CHAIR BOCCHINI: Okay. All right, so we're going to start this session with an update on the Mucopolysaccaridosis I, MPS I, condition review.

And to present this will be Alex Kemper. Dr. Kemper is a general pediatrician and director of the program on Pediatric Health Services Research at Duke University.

His research focuses on the implementation, evaluation of screening programs for children including newborn screening, screening for visual impairment and screening for lead poisoning.

Dr. Kemper is also deputy editor for Pediatrics, the official journal of the

American Academy of Pediatrics. And he now leads the condition review work group.

Before I turn it over to Alex, I just want to mention that during the last meeting we had agreed to look into what process would be needed to take a condition off the roster.

That was also one of the tasks that we needed to do, but after careful consideration and the things that were kind of backed up because of our efforts to try and strengthen our public health impact assessment, I decided that we need to first complete these things before we tackle that issue.

So we're going delay dealing with that until after we have completed the full review of MPS I and ALD and get a final vote by the committee on those two conditions.

And then we'll tackle the process of removing a condition from the roster. So Alex, we'll turn it over to you.

DR. KEMPER: Thank you very much, Dr. Bocchini, members of the advisory

committee. I'd also like to thank you for allowing everyone to stop for lunch instead of going into this because, for a couple reasons.

One, now everyone's energized, and the other thing is I think that the presentation I'm going to be making to you over the next little bit are all really intertwined.

And so the approach for this afternoon is first I'm going to be talking about MPS I. And much of this is review from our discussion of MPS I from before.

And they're just some very particular things that I want to highlight. The second thing is I'm just going to talk a little bit about X-linked Adrenoleukodystrophy.

And then I want to spend much more time talking about where we are with the public health system impact assessment and would really value feedback from you all before we begin with this process.

So I want to to acknowledge the

stalwart members of the condition review workgroup, which now has one new member, Jeff Brosco, who's a pediatrician and bioethics, who also does a lot of Title V Work in Florida.

And I would also like to thank Drs. Botkin and McDonough who have served as liaisons to us recently through the process of MPS I and have really be very helpful as we think through some other issues as well.

So first, again, I want to highlight some issues, as I said, about MPS I. I think the material that you have in briefing book is just a little bit outdated.

But again, I'm just going to be hitting the key things. So if you recall, MPS I is an autosomal recessive lysosomal storage disorder caused by a deficiency of a particular enzyme, IDUA enzyme.

It's a progressive, multisystem disorder. It has variable clinical presentations, like many of the conditions we talk about, happen across the continuum.

The prevalence, if you look at reports based on clinical detection, is around one per 100,000. However, the prevalence is higher if you look at the population-based screening studies that have been done, somewhere between three to six in 100,000.

Then, of course, that always happens with screening. You begin to detect a different spectrum of illness as well.

So in terms of the classification, Mucopolysaccaridosis Type I, MPS I. It's really two or three syndromes depending on how you think about it.

And it's heterogeneous and overlapping, and so there's the severe form and the attenuated form. The attenuated form, historically, has been broken up into, well, for the several forms it goes by the eponym Hurler.

And the attenuated is depending upon how attenuated is. There's the Hurler-Scheie form or the Scheie group and for simplicity and

clarity, I am really going to try to keep to severe or attenuated form, instead of Hurler, Hurler-Scheie or Scheie form. The severe form has onset by year and is rapidly progressive. It is multi-system in terms of the effect. The key thing for this group is that death occurs in early childhood. As opposed to the attenuated form which can have onset that is more variable. Sometime after 2 to 3 years of age up until 12 depending on which group. This can have death by teens or 20s or death later in life.

And as I go ahead, please feel free to stop me if you have a clarifying question. These are data from the MPS I registry. These are our published data.

And the issues I want to highlight here is just first of all the distribution of diagnoses in the registry, which it's about 57 percent in the severe form and the rest of course being the attenuated form.

I think on this previous slide I

forgot to mention that unlike some of the other conditions that we talked about, the severe form predominates.

Three quarters or 80 percent is the severe form. And, again, you can see the age of onset is younger with the severe form, and the median age of death is older.

In terms of these cases, which again are mostly clinically detected, treatment initiation for the severe form, the median age of diagnosis is around one and a half years of life as opposed to the attenuated forms, which can range from 8.6 to 17.1 years.

Again, for this group I want to really make sure that we pay attention to the severe form, and so you can see the median age again is 1.4 years.

So with newborn screening we can really move diagnosis earlier, potentially. So the screening test itself is based on IDUA enzyme activity in dry blood spots.

There's several different ways of

doing it, tandem pass specs versus fluorometry.

Establishing the diagnosis is primarily based on IDUA enzyme activity, which can be measured in a variety of different tissues like leukocytes or fibroblasts.

The IDUA activity will be less than 1 percent. One of the challenges is that the enzyme activity alone does not necessarily predict the phenotype.

You can have increased urinary glycosaminoglycans, which is again supportive of the diagnosis. And the genotype can help if it reveals a known mutation.

But one of the challenges that most of the mutations are private or within specific families, a new mutation. So there's more than 100 known MPS I IDUA mutations, many of which are unique to specific individuals, as I said.

In terms of known IDUA, I'm sorry. There is an IDUA pseudodeficiency mutation as well. Historically it's been considered rare.

Although, with newborn screening,

there are cases of pseudodeficiency that are being diagnosed or identified I should rather say.

And there's some question about whether or not pseudodeficiency might be more common in certain populations, such as in African Americans.

Again, there's a lot of working going on around the genotype, phenotype correlation, but this is still an evolving area.

Treatment strategies, as we discussed before, include stem cell transplant enzyme replacement therapy and enzyme replacement therapy on its own.

So you can have one, the combo or only the other. The challenge is that enzyme replacement therapy doesn't cross the blood brain barrier.

So if you have the severe form that's associated with neurologic problems, the enzyme replacement therapy on its own is not helpful.

So the idea behind stem cell

transplantation is this allows individuals to produce their own endogenous enzyme. And so it is recommended for individuals with MPS I around the year or certainly by the age of two years.

And there's an international consensus statement and the subsequent European consensus statement that talks about indications for stem cell transplants.

But really the idea is to get it done by two years of life. Now the enzyme replacement therapy has been proposed as the bridge to stem cell transplantation.

And again, we're talking about the individuals with the severe form. And there's a thought, too, that it may augment enzyme availability after transplantation while you're waiting for the new cells to produce the enzyme.

So enzyme replacement therapy on its own without transplantation is really what's used for the attenuated forms, again, because there's less of a concern about getting it into

the, past the blood brain barrier.

So I don't want to spend a lot of time, but this is our traditional approach to the literature review. And you can see that we came down with 194 articles as of August 2013.

And we've gone through and updated this, and there are about another 91 reports to add in that we're busy working on.

Some of these won't make it through the review process because they won't meet our predetermined inclusion or exclusion criteria. I don't want to belabor that point.

What I do want to talk about is two things. I'm going to step away from the microphone.

(Off microphone comments)

DR. KEMPER: -- the other data that I'm going to show. Just before we broke for lunch I got hot off the press updated numbers. So I want to make sure to at least put them in the record.

So Missouri is in the process right

now of conducting a pilot study. So it's, this is an important nuance. So they're doing full population screening.

But they're not; it's not being reported through the usual newborn screening channels. So they're still considering it a pilot study. And this began in January 2013.

They're using the digital microfluidics platform. They've screened 117,000 newborns, and of those newborns, there are 57 that were reported out as positive.

So there was one case that was confirmed to have MPS I. I don't want to spend a lot of time talking about the outcomes of this particular case.

But I do want to point out that this child did die of complications related to stem cell transplantation. So it's a very complicated case and sort of goes beyond what we can talk about right now.

But it does, I think, highlight that stem cell transplantation is not to be taken

lightly.

There were 24 cases of pseudodeficiency, of which two were genotypes of unknown significance for several months while this was being sorted out.

Now from talking to the laboratory experts in Missouri, they think that they have a process to continue to decrease the number of cases of pseudodeficiency that are identified through screening.

They began with a threshold that was significantly high that these cases of pseudodeficiency came through as positive. But they think they can dial that down to improve the specificity of screening without missing any cases.

And so one of the things that we need to go back and look at is really the time trend and seeing whether or not changing those thresholds really would have gotten them out.

But they feel very confident about that. There were three carriers that were

identified, 24 false positives. There are four that are still pending work up.

And one child was lost at follow up. So the overall false positive rate is 0.49 percent. Now there is in-house repeating on the same sample that happens before newborns reported to have a positive test.

And that's around one half of a percent right now. So it's not like one half of a percent are being recalled for new blood spots. But those are the blood spots that are being reanalyzed.

So I mentioned before about how there's thought about the, that they can lower the IDUA cut off level to decrease the number of cases and see the efficiency that are identified.

So this is, I think, really important data. Does anybody, I almost hate to say this. Do you have any questions about this that I can answer? I want you pay attention to the nuance.

MALE PARTICIPANT: It's not so much; it's really not a question. It's a comment. If you remember Piero's talk earlier, they are not just looking for MPS I.

They are looking for four other LSDs so they could do multivariate analysis and create some ratios and therefore reduce the, at least the in-house repeat rate probably dramatically.

And if they were to consider not just the other LSDs but the amino acids, acylcarnitine, collect the results, et cetera, they control, get it down even further.

DR. KEMPER: That's an excellent point so that these new strategies to reduce false positives and newborn screening. And certainly they should be applied to this.

So here are the Illinois data, and I'd like to thank them for emailing me like what seems like minutes ago. So this is considered by them to be a validation study.

They are screening actual babies

though. This isn't just anonymous dried blood spots. So I'm going to change some of these numbers.

But they've screened almost 12,500 specimens, 12,404 for those of you who like to be exact. And there were 20 that were repeated in-house for low IDUA cut off.

And then there were seven that were reported out as positive. Now this is what I have now for the ones that were presumptively positive.

And this replaces the numbers that are here. Four of them had pseudodeficiency. One was normal and therefore false positive. One was a carrier, and there's still one that's pending.

So in the, what is it 12,000 cases or 12,000 newborns that they've screened so far they haven't detected a case yet. I'm now going to just repeat myself.

But they've identified four babies with pseudodeficiency, one with the carrier,

and there's still one being worked out. And I can't comment on the one that's still being worked out.

So more information to come. Any questions about that?

MALE PARTICIPANT: For the pseudodeficiencies are they healthy?

DR. KEMPER: Yes, that's amazing. Family medicine is allowed to ask same question twice. So I've always had a lot of respect for family medicine.

So there is no significance of pseudodeficiency that I'm aware of, that these are healthy newborns.

Now thinking back to when we were talking about pseudodeficiency with Pompe disorder, there was a question about if you had on one allele the pseudodeficiency mutation and then on the other allele some mutation associated with the condition whether or not they potentiated each other and made the condition worse.

But really, as far as I know, our readings about MPS I and from talking to experts, the pseudodeficiency is not associated with any disease.

CHAIR BOCCHINI: Let me just ask that if, when you ask a question please state your name first so that we have it for the recording.

FEMALE PARTICIPANT: Right, and Dieter, some other lab person might want to correct me if I'm wrong, but there is a, it's sort of a technical term here.

If you truly are deserving to be called pseudodeficiency allele, what that means is in the laboratory it looks like it doesn't work, but in the person it does work.

So when the term pseudodeficiency is used properly, it means that the person is healthy. Is that correct, Dieter? He's nodding. Pseudodeficiency used properly means the person is healthy.

DR. KEMPER: So just from a very

high level summary about IDUA screening, the study said that IDUA activity can be measured, and there are a variety of different ways of doing it.

I think it's fair to say that the screening algorithm is still being refined to balance case detection with these issues of false positives and pseudodeficiency.

And the big challenge is related to predicting the formers of severity for those cases that are detected.

All right, let's talk about treatment, focusing in on severe MPS I. So these are the children that get, have a stem cell transplantation.

So if you look at stem cell transplantation compared to historical controls, it's associated with increased survival up to 65 percent to ten years versus less than 5 percent, preserved development and improved mobility.

There's little evidence right now

regarding stem cell transplantation in asymptomatic infants.

And one of the things that are evidence group needs to do is now that more time has passed in the various states instead of doing pilot studies is to go back and talk to the experts to see if there's any more unpublished data about it out there.

It does appear that early treatment is likely better, but the ideal timing is unclear. And so sort of figuring this out in relationship with the current clinical guidelines, I think, is going to be important work.

And again, there's, it's typical now that enzyme replacement therapy is given prior to transplantation and figuring out what the additive benefit of that is, is going to be important work or potentially harm if do antibodies, I guess.

In terms of the attenuated form, enzyme replacement does lead to improved

outcomes. And there is a randomized trial, but this is in adults who developed symptoms.

And those outcomes are based on mobility improvements on the six minute walk test and a disability index.

The role of enzyme replacement therapy in asymptomatic attenuated MPS I is unclear. I can't comment on that.

And then in terms of the harms of treatment, if you remember back at Pompe disease it's the same thing where you need have chronic infusion.

And then there is a risk for antibody development, and I can't comment on how frequently that happens now. But that's something that we're trying to sort out.

So we have a lot of remaining questions that we will come back to you with. Answers to some of these hopefully, related to pseudodeficiency and whether or not they're subpopulations that are more likely to have pseudodeficiency, issues of predicting the

severity or the form, what to do about or what's known, I guess I should say, about genotypes of unknown significance and earlier identification in the attenuated forms.

What are the implications? What's the importance of earlier initiation treatment for severe MPS I, that is, is there a critical window that we should really be striving to capture?

What about these other treatment approaches to address brain involvement? There's some questions and some work out there around intracecal and subreplacement therapy for that's injecting it directly into the cerebro spinal fluid.

Then of course we need to talk to those who are actively engaged in screening for MPS I and then going back to the well to look at the MPS I registry directly or looking at other unpublished data.

It's a lot of stuff. So right now what we are doing is we're finalizing the

evidence review, and I talked to you about how there are some 90 more articles out there that could potentially be included.

My guess is that only some of them will. We are working closely with Lisa Prosser at the University of Michigan to do this modeling around the population benefits of screening.

So if you were to implement this at a statewide or a national level, how many cases would you detect and so forth?

We are going to be assessing the public health system impact, which originally I was going to say after lunch we'll talk about, but after a couple slides we'll talk about.

And then, of course, finalizing the condition review report. So that's where we are with MPS I. I'm going to change gears a little bit. Does anybody have any comments on MPS I? Okay.

(Off microphone comments)

DR. KEMPER: So, Dr. Green's

excellent question was whether or not there's a risk that individuals who have the attenuated form might get transplanted.

So, of course there's always a risk when you identify people through screening that that might happen.

When I talked to the experts, and again, this is one of those things that we need to go back to the experts for, there are these international consensus guidelines on what constitutes someone with MPS I that ought to be transplanted.

And that is based also on neurologic exams so that these children are not completely asymptomatic. As well, they do look at enzyme level.

And the children with severe MPS I really do have about as close to zero enzyme activity as you want.

So this is something I'm going to come back with more answers from the experts for you. I think that the potential is there

because it's a human process that that could happen.

I can't, I would think the likelihood of that is low based on the opinions of the experts I talked to about it so far.

But it's clear that it's not an easy thing that one can diagnosis purely by laboratory standards. Does that answer your question?

CHAIR BOCCHINI: Carol Greene?

DR. GREENE: So, as Debbie already knows, this came up at Maryland just the other day. And not being one of the experts that's, I'm not an expert in MPS.

I would say there's, if you're seeing somebody who knows anything about MPS there will not be a kid transplanted who doesn't need it. They're obvious at birth.

They don't have neurologic disease apparent at birth, but the x-rays are different. The physical exam is different. There's subtle things, but they're obvious to the trained eye.

The kids who will get transplanted are the ones who have clinical changes evident on physical exam and x-ray at birth, and then you get a chance to watch the neurologic development.

Barry is nodding, so yes, all of the clinicians; we're not worried at all.

DR. KEMPER: I mean just for the record, because I just want to say these kids aren't obvious on exam at birth because it's not like the primary care physicians are missing obvious things.

These are things that upon further investigation, but without a screening test one would never pick up someone with --

DR. GREENE: I need to agree with that completely. It's fair. It is, and that's why I said obvious to the trained eye. So it is subtle, but it is --

DR. KEMPER: I just, I think it's an important thing not to, just for the record, I think that given a bunch of newborns an expert

in MPS I wouldn't be able to identify it without the benefit of some sort of laboratory testing.

(Simultaneous speaking)

DR. GREENE: For the record for MPS I, I have to disagree. When we go back and look at newborn pictures of the babies we see it.

So, and the moms will tell us that they've been complaining to the pediatrician about the shape of the back since birth.

So given a positive screen we will be able to distinguish between the babies who need the treatment. It is absolutely not obvious to the pediatrician.

Nobody would expect a pediatrician to pick it up, but given a positive screen we can distinguish between those who need a transplant and those who do not.

DR. KEMPER: Okay. I can live with that, sort of. All right, so let's move along. So we have begun our work on the X-linked Adrenoleukodystrophy.

And I don't want to spend a lot of

time talking about this because we're still in the evidence review process, but I did want to talk a little bit about it.

So, the overall presence of X-linked Adrenoleukodystrophy is expected to be in the order of about one in 20,000. It comes in three different forms or types.

There's the childhood cerebral form, which typically comes to at least clinical attention between the ages of four and ten.

And as you heard before lunch, unfortunately, survival is very short after individuals become symptomatic.

Then there's this adrenomyeloneuropathy form which has onset in early to mid-adulthood and then a form that's associated with Addison's disease.

Only those are individuals who rely on supplementation for their Addison's disease but don't necessarily go on to develop the other neurologic effects.

So to tell me, interestingly, from

the stuff that I've read it does look like those individuals with the Addison's disease only really do sort of presage the development of some sort of neurologic problem later on.

So I think, like all the other conditions that once you start looking at them they're very complex and overlapping.

So the genetics of this condition, it's related to mutations in the so-called ABCD1 gene, which produces the Adrenoleukodystrophy protein.

This protein's job is to transport long chain fatty acids into peroxisomes. Because of that you develop all the findings that we've talked about, including there's a strong oxidative entry to the affected individual.

Interestingly, from some of the stuff I've read it looks like because of the association with transporting into the peroxisomes that it might be able to pick up some other peroxisomal disorders, none of which I'm

expert enough to talk about this morning.

This is a condition that poor genotype-phenotype correlation even within families, so predicting disease courses is challenging.

There's the dry blood spot work that's been conducted at the Mayo Clinic, and we heard also about the New York data. I don't have those for this morning or this afternoon.

Diagnosis is based on mutation analysis. At least you know that there's a mutation in the gene measurement of very long chain fatty acids.

And then for those children that are going to have, or individuals I guess I should say because it can happen older, who are going to have neurologic problems.

There's a scoring system, the so-called low score that's based on findings on MRI that can be helpful in terms of establishing the diagnosis and also predictive.

And the treatment is, as with many

of the other conditions we've talked about, stem cell transplantation, adrenal hormone replacement therapy, including stress dosing for those who have the Addison's form or have their adrenal gland affected.

And then I was reading, too, that N-acetyl-L-cysteine has been reported to be used. Now that's a drug I always, clinicians used to treat kids who've had acetaminophen poisonings.

But it turns out that because X-linked Adrenoleukodystrophy is associated with these oxidative injuries that N-acetyl-L-cysteine can help reduce the oxidative stress associated with the disease.

So there are treatments out there, and again, we're going to be going through looking at the net benefits of early initiation treatment for those individuals who are identified through screening.

I'm going to move and switch gears again unless anybody wants to make another

comment about X-linked Adrenoleukodystrophy.

Okay, last time right, just as I was about to hit the arrow somebody asked me a question, so I'm going to go really slow. Yes, okay, because I knew it was out there.

CHAIR BOCCHINI: I think we're good. We can ask then if there's any quick questions.

DR. KEMPER: Okay.

CHAIR BOCCHINI: If not, go right ahead.

DR. LOREY: I have a quick, this is sort of a question.

CHAIR BOCCHINI: We hear you. Go ahead.

DR. LOREY: Yes, maybe you said this. I'm sorry. What's the mortality rate from the stem cell transplantation and bone marrow transplant for both of these disorders, MPS and, or is there any?

DR. KEMPER: I'm not sure if I understood that.

(Off microphone comments)

DR. KEMPER: I can't comment on the mortality rate from stem cell transplant for X-linked Adrenoleukodystrophy or stem cell transplant in general.

There are data in there regarding the risk of mortality from the MPS I registry, and I don't know what those are off the top of my head. But I could tell you that's sort of built into the stuff that like Lisa Prosser's doing.

And if you want, Fred, I could email you once I sit down later at my computer.

DR. LOREY: Okay, that would be compared to (inaudible).

CHAIR BOCCHINI: Could you repeat that, Fred? It wasn't clear.

DR. LOREY: Sorry. I was mainly curious as how that might compare to Krabbe, for example. It's a lower --

DR. KEMPER: You mean in terms of the risk of mortality with transplantation?

DR. LOREY: Yes.

DR. KEMPER: I'd rather pull the numbers than --

DR. LOREY: Okay. That's fine.

DR. KEMPER: I would expect that the mortality rates are going to be similar, and I can comment to the, most of the publications that are out there don't follow individuals after transplant for very long simply because transplantation hasn't been available for very long.

But unless somebody wants to correct me, otherwise it seems like the mortality associated with stem cell transplant is an earlier effect not a long-term effect.

So once you engraft the mortality, your risk of death goes way down except for GBH or if you have something like what happened with that other child who had MPS which was chronic CMV infection.

I should have hit the arrow faster.

CHAIR BOCCHINI: All right, no

questions from the table. Then --

(Off microphone comments)

DR. KEMPER: Right, and that actually matches up very well, I guess I should say that, too, with the Pompe disease, that if you go into the transplant healthier, your risk of survival is much better.

It's an excellent point. So I need to wait for the --

(Telephonic interference)

CHAIR BOCCHINI: That was bad.

DR. KEMPER: Okay. There we go. I have to say. I'm glad I figured out how to put things on full screen because there's nothing that makes it harder to talk than when you see your own words coming up on the screen.

And now I'm like waiting to see if that happens. We can, okay. Fortunately, all right, so this is really where we in the condition review workgroup would like to get advice from you all in particular.

Of course, we're always welcome to

advice, but we are really looking for advice here about how to assess the public health system impact of adding a condition to newborn screening.

So let me recap our history. So in 2012, we had an EAP as K.K. Lim likes to call them. Those are expert advisory panel meetings to develop the decision matrix, which I'm going to show in a second.

Then that led to work in 2013 and 2014. In 2012 we pilot tested a Public Health System Impact Assessment for Pompe Disease, and that was overseen by my good friend and colleague, Jelili Ojodu, through APHL.

And that was based on really in depth interviews with representative states. I'm turning my volume up. Okay. Hopefully, I wish you could turn up my intelligence, too.

So in 2014 we had EAP Number 2 to develop the Public Health System Impact Assessment approaches. And we've discussed at this group before about the importance and also

the challenge.

Now we're coming back with a way forward for MPS I. And, but before we get into it, the thing that I really want everyone to keep in mind is that at the end of the day we have to be able to support the work of the advisory committee in terms of putting things onto the matrix.

And so they're two broad things. There's the issue of feasibility, which you on the advisory committee have to rate either as high or moderate versus low.

And there are issues related to feasibility like the established and available screening tests and approach the diagnostic confirmation, an acceptable treatment plan and the ability to provide long-term follow up with whatever that's involved with.

That's the issues of feasibility, okay. And a lot of that information will come from the work that we're already doing in terms of evidence review and talking to the experts

in the modeling and that kind of thing.

Okay. So the second issue, which is really challenging, is this issue of readiness. And if you remember the matrix, which I'm going to show you in a second, it can be broken down into ready, developmental readiness, or unprepared.

And this red sentence here is from the material that you all have agreed to before, which is the readiness comes into play after the state makes a decision to include the condition and that there's funding available.

So if all the stars came into alignment to implement the test, how long would it take you to do it, and what would be the things that would hold you back?

Okay. So what I want to do, again, in an interest of the time is just highlight again here for, to be ready it's most newborn screening programs could implement it within a year.

Developmental readiness is between

one and three years, and being unprepared means that if all the stars came into alignment, it would take more than three years to do.

Okay. So I want everyone to keep that in mind. Any questions about that? All right, so here is the matrix.

And so the work that we did in the evidence review process allows you to make decisions around net benefit.

So is there a significant benefit? Is there a small benefit, a negative benefit? How certain are you about that?

Those things, once you get through with assessing the net benefit, then the Public Health System Impact Assessment, which is the columns on the right, which I've labeled PHSI, come into play where you have to just assess whether or not something's high or moderate feasibility or low feasibility and then look at readiness.

And that gets you into A1, A2, A3 or A4. One of the things that we haven't talked

about, or I don't know, Dr. Bocchini you want to comment on, is if the advisory committee goes through the process and happens to find that a condition is associated with zero to small benefit or negative benefit or there's like enough uncertainty that you're not up in that significant benefit, high certainly category, what you would like from the condition review workgroup around doing the Public Health System Impact Assessment because in a sense it wouldn't really matter in terms of the recommendations that would come out of the group.

I don't know if you want to comment on that now, or I'm going to distract people.

CHAIR BOCCHINI: Yes, I think we can. I think that the important thing is that the way we've set up the review; there are two members of the committee that are part of the condition, specific condition review.

And I think as the data becomes available, we do plan for significant interaction between the condition review

workgroup and the full committee.

So if it looks like there's developing evidence of harm or no net benefit, then I think those committee members can help inform the full committee.

And a committee decision can be made as to whether to proceed to a full public health impact evaluation, or based on the available data, bring evidence to the committee that would potentially stop the process.

So I think we could stop it in that fashion if there's evidence of harm.

DR. KEMPER: Right, and I guess I should add I'm sensitive that we were just talking about MPS I and Adrenoleukodystrophy.

I don't mean to say that I think that's the case for either of those conditions. But I just wanted to clarify.

CHAIR BOCCHINI: Correct. Steve.

DR. MCDONOUGH: I have a question on the definition of unprepared, indicated that if a state makes a decision to do it, and it's going

to take them more than three years, and as a committee, if we're going to if we're going to determine something as unprepared or states are unprepared, are we saying that most states in three years will not have implemented the screening as opposed, what the committee is looking at versus the individual state.

And one of the points I'd like to bring out is that SCID I think was recommended in 2010. And I think currently there's 12 or 13 states that are doing SCID screening, 20.

Is that when this committee which I was not a part of at that time, made the recommendation in 2010?

If we knew that 2014 it'd be less than half the states doing it, would we say that they're unprepared to do it, and we would not have retrospectively proved that?

But I think that definition of, when the committee looks at it, what's, are they unprepared or not is important.

And my perspective on the

committee's role as, if something is going to take three or four years to implement, that doesn't mean we should not recommend it if we had it.

DR. KEMPER: I'm going to see if I can do this. I'm trying to; this is something that I've thought about. So I'm going to stop the drawing.

All right, so I have to move away from this. So I've thought a lot about this, and I didn't mean to make light of it because it's actually a really important point.

So what you're saying is that if the advisory committee voted for SCID to be added and a fair number of the states, for whatever reason, haven't added SCID on, but for the purposes of readiness from the matrix, and I'll just move over here, is, the issue is once they decide to do it and the funding is made available.

And so I think that for those of you who are more familiar about SCID, I think that's

been one of the hang ups, not necessarily the readiness of implementing the test and providing the treatments and so forth hasn't been as much of the issue as much as sort of the stuff leading up to it.

But those are going to be important issues that we're going to have to bring up when I show you the survey.

I don't know if I addressed your concern, but I know exactly where you're coming from.

DR. HOMER: I guess I'm still confused about this. We make recommendations based on whether we believe, the thing is, there's evidence that it's a good thing that is if the test, if there is a test.

It can be done. The children benefit. The children will be healthier as a result of this and the aggregate population.

It is reasonable for us to assess whether states are able to do that or not. That's useful information to say yes, if we

wanted to do this, since it's going to cost a whole heck of a lot of money, you're allowed to stand for training.

But does this actually say that states say well, it's going to cost us a whole bunch of money, and it's hard. It's not in our budget, that we would actually not recommend it. Is that where we are?

DR. KEMPER: So, I hate to like speak on behalf of the advisory committee.

DR. HOMER: I know we did this. It's been a long time.

DR. KEMPER: I know we did, but I'm going defer to Dr. Bocchini, but it's not, if you're up in that A1, A2, A3, A4, it doesn't mean that there's not a recommendation that screening is beneficial.

But there are these like additional statements about what needs to be done to be able to get things moving. I don't know. Dr. Bocchini, I really shouldn't, this is going beyond what the clinician review work has done.

CHAIR BOCCHINI: Yes, I think that we obviously want to work in partnership with the states. And so that's the reason for trying to parse this out and trying to see what the barriers are.

And so I think that Alex's comment is correct, that this would not, if a condition met all the criteria that you just mentioned and the states were unprepared to do it, we would still vote that it would, to include that condition but recognize that it might take the states three or more years or up to three years to get it done once they made the decision to do so.

So this is really working together with them on a time line within which might be appropriate or states would be capable of doing so.

And so I think that's part of why we want to try and strengthen the Public Health Impact evaluation before we get to that point so we have that data. And then we can make that,

include that in the evaluation of the condition.

DR. KEMPER: Right, and states have a lot of competing demands, and so being able to be clear about the kind of resources and the kinds of things that would need to happen to be able to implement it, I think helps provide a road map and also helps people understand why things don't just happen tomorrow.

Is that fair to say? All right, I'm going to move on. All right, so there's a whole host of things that need to be considered for the Public Health System Impact, right?

So there's the ability to screen, issues related to short and long-term follow up, how newborn screening programs themselves are organized, data systems and information exchange systems both to make sure that babies get screened and that information gets appropriately reported as well as you'd have to follow them up and make sure that screening is having the expected benefit.

There's issues related to the direct

cost of screening, whether or not that be to the health department or whoever.

There are also, within public health departments, opportunity costs. So, for example, if a new condition is added to newborn screening that might have impact both within the newborn screening program itself as well as the broader public health system.

And then there are other issues that are important to consider but also hard to get to, issues related to leadership and motivation to accomplish things.

So there's a lot of potential things that could be included. Similarly, there are many stakeholders in the process. So there's newborn screening program directors, the laboratory directors, public health commissioners, state government officials, laboratory and clinical specialists, primary care providers and payers.

And of course families and the public are key stakeholders, but here we're

taking the perspective of the direct impact on the health system.

So I don't want to send the message that obviously families are the whole reason that we're doing all this.

So I don't want anybody to take home the message that we don't think that that's important but just in terms of assessing what the direct impact is on public health.

That's why we structured it this way. So we've come up with a general approach to do this. First of all, given the time pressure to really help the advisory committee come to recommendations about these conditions is that we really need to focus on the features that would drive the advisory committee decision making process.

So there's a lot of interesting and important questions, but we need to really focus on those things that are going to allow you to make a decision regarding the matrix and ultimately any recommendation to the Secretary.

We would like to consider general newborn screening issues and condition specific issues separately.

And one of the great things about that is that APHL through its NewSTEPS program already has fairly granular data on how newborn screening programs operate.

In addition, there's the regional collaboratives and so forth. So we really don't want to spend time thinking about general newborn screening issues but really spend our time thinking about condition specific issues.

Unlike last time we want to gather input from all the states and not just a representative of sample states but really allow all states to voice what the impact might be within their state.

Now we're going to stratify things. So we're going to gather general information from all states but do this sort of deeper dive within the states that have actual experience with adopting the condition whether or not they,

maybe they've tried it and aren't doing it or are in the process of doing it or actively doing it.

Any state that has actual experience because it's hard to comment on something in detail if it's not something that you've ever done before, of course.

We are going to work with a key point of contact from within each state who's going to work with others to respond to those questions.

And so I've been struggling a little bit about how to identify the best person and that's because the way newborn screening programs are organized across different states.

There are different people that are sort of knowledgeable, but I'm thinking that as a start having conversations with the various regional collaboratives to find out who within their region within the states would be the most appropriate person to lead the collection of data.

And then we want to have a standard approach to assessing all the conditions that we look at.

So by standardizing things it's going to make us much more efficient and also hopefully make us more consistent so that we can understand, not hold conditions to different standards each time we look at things and to really sort of allow understanding across the whole world of newborn screening.

And then of course we need to be responsive to the OMB requirements. I'd rather not spend a lot of time talking about OMB because it's just like painful.

But we do need to submit a package to the OMB and because of that we can't tailor the survey each time. We have to have something that's more general.

Now I'm going to separate out again we're going to talk to the states that have actual practical experience with this and do in depth interviews, kind of like what we were

doing before anyway but expanding the kinds of questions we ask.

Those things, those kinds of questions are obviously going to change from condition to condition but as a sort of first survey that goes out to all states is going to have to be something that can be reused.

Okay. Questions about our general approach? All right?

CHAIR BOCCHINI: Fred.

DR. LOREY: Remember we also agreed in the Public Health Assessment that we would contact the specialists who would seeing these patients for their opinions on whether this is appropriate or not.

DR. KEMPER: Yes, so --

DR. LOREY: Not just the states that are doing it.

DR. KEMPER: Yes, so it gets, so we'll definitely be talking to specialists as part of the general evidence review process.

If we're going to be doing general

surveys of specialists, it gets a little bit problematic in terms of OMB and stuff like that.

So we're going to be, as we've done before, talk to a broad range of specialists to find out what their experience with the condition is and what their attitude is and so forth and then be able to do the deeper dive within the states that actually have experience.

So I agree with you, but I just want to put that nuance in so I don't get in trouble. Does that make sense?

DR. LOREY: Yes, sure.

DR. KEMPER: Okay. So I figured at this point in the talk everybody would need to have something to laugh at, so I put this.

I know this is like a difficult thing to think through, but I do think that it reminds me that we want to keep things simple.

I think it's my history in math right there. Actually, I have some worries. I don't want to give them away.

So let's talk about the data collection approach and sources and Fred that was a nice transition into it.

So there's general issues related to the process for adding conditions to the state panels, existing newborn screening infrastructure, laboratories, workflow, that kind of thing, laboratory and reporting systems, general approaches to short and long-term follow up and their requirements.

So states have different obligations in terms of what they're required to do in terms of long-term follow up and provision to treatment and that kind of thing.

So having that as by way of background is going to be important, and again, I've mentioned before.

But through Dr. Sontag and Mr. Ojodu work with NewSTEPS we'll be able to get to a lot of this information. Of course we can also rely on the regional collaboratives.

Now in terms of the condition

specific newborn screening issues, there are data elements out there, some of which we're going to be able to get from the review again, things like the existence of validated screening methods and whether or not they're high throughput, laboratory follow up, systems reporting, diagnostic confirmation, short and long-term follow up needs and the need for treatment centers and whether or not clinical guidelines exist.

A lot of that stuff we already had before and can come from the evidence review findings. Some of this, and I'll show you in a little bit, are going to be coming from surveys of the states and then the in depth interviews.

So this is just to refresh everyone. Okay. There are three components to everything that we do. There's the systematic evidence review.

There's the modeling of the population benefit. Okay. Those two parts right there alone are going to get a fair amount

of the information around the public health impact.

But then we're going to drill down deeper with the Public Health System Impact Assessment that we're going to do with states.

We'd like to be able to complete things in nine months, and there's really a lot of cover in a short period of time. So we really have to be efficient and keep things simple and straightforward.

Again, I thought everyone would need a laugh at this point in the day. Being fixed elements, two polar bears, three, no four seals. Okay.

But I do think that what I'm going to drive home is that there are things that are needed to make decisions. And we need to just focus on them. Okay.

So here are the actual steps. Okay. So we're going to be working with the regional collaboratives to find out which states have or are anywhere in the process of screening or

planning for the condition.

And we need to do that really early because we want to be able to do start interviewing those people and collect unpublished data right away.

Okay. And then we need to, I'm going to finish this slide and then go back to the questions I have. Identify the most appropriate survey respondents so that you can synthesize across the state and let us know what's going on.

Then, one of the things I feel strongly about is that we can't have these respondents answering questions about a condition, an often rare condition that they don't really know anything about.

We need to be able to easily educate these respondents so that they understand what the condition is about both in terms of the condition itself, the benefits of screening, early intervention and so forth.

And so there are two things that

we're going to produce. One is a fact sheet.

And thanks to Anne Comeau and Susan Tanksley for helping us to put things onto like a one or two pager that's everything that you would need to know from a public health department in terms of the, what's the process for screening and whether or not if the kid, if there's available quality control things, how fast it would take to do, what kind of equipment you need to do, how many babies need to be recalled for other screening and what's involved with diagnosis, all those kinds of things.

And our goal is so that the respondents can have the standardized information in hand at the time they respond to the survey because, again, we want people to really give us informed answers.

The other thing is that we're going to record a brief webinar. I'm thinking like a, I say 15 or 20 minutes, but I'm sure it will go longer than that because I always do.

But, and to record it so that if someone with similar data, they could go to that as well. So I think that we want to at least make that information available to the respondents. Okay.

Then we need to field the survey. I'm going to show you a survey. The thing that you have actually, I think that you have in your documents is old.

It needed to be simple. It needed to be, focus us on what the advisory committee would need to make a decision. It needs to be reusable. Okay.

And then, again, we're going to do the deep dive with the other states. I know I'm being repetitive here, but I just want to make sure that you understand what the process is.

Maybe I'll be quiet for a second and think especially for those of you who are involved in the newborn screening program in your own state if you could; they're different kinds of people that we could talk to.

So we could talk, we could have the person who oversees the public health laboratory that oftentimes they're not newborn screening specific people.

We could talk to the people who oversee the particular newborn screening lab. Some states send their screening to another laboratory there in another state or a private lab and that kind of thing.

So figuring out and being consistent about the kind of respondent that we get, I think, is challenging.

And it needs to be somebody who's committed to kind of looking not just within their newborn screening program but sort of more broadly.

I know, Mike, you've done this kind of thing in the past or if you have any, I didn't mean to poke on you. But you looked at me, so I --

DR WATKINS: Well, no, I think if states are to have advisory committees, newborn

screening advisory committees we'd probably have the requisite knowledge base to address some of that either with or on behalf of their states.

But I don't know. That's not all states that have an advisory panel. I don't even know what the proportion is anymore.

DR. KEMPER: Yes and the expertise is probably variable, too. I don't know. Yes, but I mean so --

DR WATSON: The advisory committees, I think, are broadly representative of the kinds of things that are in newborn screening. So it would have to be a brand new type of specialty area of screening, throw them off.

DR. KEMPER: Does anybody have any other thoughts? Okay, well, we at least, I mean if we, and fortunately APHL is going to be helping out on this.

But I think even if we reach out to like a similar person in each state if they could

tell us who could answer. You're worried that people aren't going to answer?

All right, so when you see the surveys come out, and there's an N of 1, you'll know that's Hawaii.

FEMALE PARTICIPANT: Or Alaska.

DR. KEMPER: Or Alaska, okay. There's two little islands next to each other in the corner. So the, one of things that I think we can be clear about and that I can rely on the advisory committee is well is to incentivize states to respond to this.

I mean states are free to choose whether or not they reply, but I think that the opportunity to weigh in something that could have significant impact on their health program might motivate people.

This is something, we're not going to resolve this, I guess, in the next minute but I would, on behalf of the condition review worker, we would value any particular advice you have, Dr. Bocchini.

CHAIR BOCCHINI: I was just going to say I think the first time we do this it's going to be a little more difficult because it would be finding the right people in each state and finding the people who need to answer the various questions in the survey.

But I think you're right. I think if we make people aware of what the goal of this is, I think that we should be able to get states to be involved in this process.

And so I think once we figure out who to talk to and how to get the information back in a timely fashion in each state from the different parts of the newborn screening program I think that'll make things easier once you establish those contacts.

DR. KEMPER: I'll defer to the chair. There are some other people with their hands up. People outside the table we need, please if you'll give your name. And then we'll need to repeat the question if you don't go upfront to the microphone. But Cathy?

MS WICKLUND: So I'm just going to get back to Sylvia's comment for a second. If the committee is going to pass something regardless of the readiness for a state, is the motivation still there of the state to provide the information if they feel like ultimately it isn't going to affect our decision making process?

Is it enough motivation to think that in the report we're going to address the time line or address the specific needs that they might have to move forward?

DR. KEMPER: So that's a Dr. Bocchini question.

CHAIR BOCCHINI: I think it is, and that's why we want to provide, we want to get the feedback because that will influence where the condition ends up on the listing.

So I think if it ends up as an A, it's going to be based on the fact that everybody's aligned that this is a condition that has benefit and that it can be done.

But recognize that there could be barriers that need to be addressed before timeliness of initiation and/or implementation.

But I think if it becomes very clear that this is something that cannot be addressed, that changes where you're going to put this in the matrix.

DR. KEMPER: Right, especially if --

(Simultaneous speaking)

CHAIR BOCCHINI: Yes, I think that the input will influence the outcome, and I think that's the goal. Does that answer?

DR. MCDONOUGH: When we had this debate a couple years ago and there wasn't a unanimous vote on the committee. But the only ones that were no brainers were going to go through are A1s and A2s.

The A3 and A4, the committee would discuss further, and they would be interested in demonstration projects to decide if they

would go forward to make it an A1 or A2.

And I was concerned at that vote that we were slowing things down too much and making things too restrictive to add conditions that states could eventually do.

And that's a philosophical what is the role of the committee. And there's different opinions on that, but if it, and the point I would want to bring up here is that if given this matrix for your given SCID now, that that would've been a A3 or A4.

And we would not have approved SCID in 2010. There would be some more research projects and it would come back a year or two later.

And there would be some kids who would have died of SCID if we had not, if the committee at that point did not approve it.

And I'm concerned as we go forward here that again, that we don't put too many barriers here to slow things down that adversely impact children and families' health.

CHAIR BOCCHINI: I think that's a really good point, but I think SCIDs decision was made just as I came, I think Jeff and I were just coming on the committee at that time.

And I think people who have been around longer can correct me if I'm wrong, but I think SCID was, in fact, delayed initially because of the fact that there have not been a patient identified.

So it did come to the committee, and it was held until there was adequate data. When it came up the second time because there was data, it was approved by the committee.

And I think when we first put the matrix together; Alex did use SCID as one of the conditions that went to test this matrix.

And it was clear that the same decision would have been made at that time using this matrix, so I felt pretty comfortable that the matrix did, in fact, reflect the activities of the committee.

And so, and again, I think it's more

difficult to try and take something that we don't have a specific entity about and then try and fit it into this.

But I think when we looked at SCID, and I think, Alex, there was one or two other conditions that you looked at that the committee had made a decision on.

And it looked as if the decision would have been the same at that time based on use of the matrix.

DR. KEMPER: That's correct.

MALE PARTICIPANT: Got a few old faces, right?

CHAIR BOCCHINI: I'm sorry. We got Dr. Lu first and then Fred.

DR. LU: During our previous discussions about the Public Health Impact Assessment, we talked about the need to look at cost/benefit at the population level.

For example, for every $1 invested in MPS I screening, we'll end up saving $3 or $4 in long-term care costs and so forth.

Or how much for the cost per life saved or how much for the cost per year of quality life? I have not seen anything here that's going to lead to that information that would help --

(Simultaneous speaking)

DR. KEMPER: Shoot, I can't get rid of that thing. I'm looking for the slide right now. So, we do want to look at that and so to the degree possible.

So right, so oftentimes, and this came up for example around critical degenerative heart disease where there's a lot of talk about if you identify those babies and provide them their surgery earlier if they're going to have less costs down the road.

So we do, I'm sorry. I'm like, okay, so if you remember, there are three components to this, the systematic evidence review, the population benefit.

And then this is where I see that modeling come in. We didn't do as much modeling

in the past as I think that we can do moving into the future.

And part of that is we did the modeling really at the, once the systematic evidence review part was done and that things were really getting ready to a vote, and it was more, it was helpful to provide information on the number of cases that might be picked up and that kind of thing.

But to get to this population net benefit from all these different metrics, my plan was by doing the interviews with the states that are actually doing things, we can get to that level of information.

It's hard to get to a lot of the costs related to treatment, so I don't want to over promise that we can say like oh, if you were to screen for this condition it's going to be cost-neutral or it's going to be $100 per case detected or whatever.

But I do think that we're going to be able to provide the advisory committee with

a much better sense of it. So, for example, thinking back to Pompe Disease.

We had information on the cost of enzyme replacement therapy, but we didn't really use that to show what the effect might be on the payer over the life of that individual needing the enzyme replacement therapy and those kinds of things.

I think that by sort of back loading when we get the information for states we'll be able to provide some of that information.

I think that a lot of the information regarding sort of the lifetime benefits is going to be really hard to get to though. So I would be cautious about not over promising the degree to which we can do that.

And part of it is a lot of the treatments are being developed. The screening happens, in these cases, are detected.

But at least we'll be able to point out where the areas of uncertainty are. I know that's like 100 percent satisfactory, but I just

don't want to over promise what can actually be done.

DR. LU: Sure, I guess I'm just a little concerned that if we just saw and provide, and just saw the information about the costs of screening and not really looking at the costs of not screening or the savings from screening.

Then you actually have a pretty skewed view of population level costs that may distort the decision making by the committee.

DR. KEMPER: Right. And since like figuring out both the denominator and the numerator as well, too.

You know what I mean, like it's going to be challenging to figure out the costs and also the expected benefit over the lifetime of the affected person.

I mean, so just to kind of like drill down to brass tacks, like if you think about Pompe disease there is this large group of individuals who are going to have late onset

disease.

And they're going to have to be followed to some uncertain time, and at some point they're going to need to get enzyme replacement therapy.

And that's a potential cost there, but I don't know how we could reliably get to it other than to say the advisory committee that, like look there's this many people.

And then they're going to need all this kind of stuff. And then with Pompe Disease, it would be easy to figure out what the lifetime cost of the enzyme therapy would be at current costs based on the estimated weight of the child and so forth.

You can come up with at least bounds around that, but there are problems, too, about what the long-term benefit is for that particular child because there are some questions about plateauing in terms of the neurologic development and those kinds of things.

So it's really, really nuanced. And I can promise you that we'll do our best to get to this stuff, but I think that there's always going to be questions about the validity of the estimates.

I just want to see, like you know what I mean. I don't want to over promise and under deliver. I like it the other way around.

CHAIR BOCCHINI: Okay. I have Fred Lorey on the phone, Jeff then Coleen, and the question from the back. Fred?

DR. LOREY: I no longer have my questions. I withdraw.

DR. KEMPER: Did I anticipate your question?

DR. LOREY: You did.

CHAIR BOCCHINI: All right, defer to Jeff. Go ahead. Jeff?

DR. BOTKIN: So it seems to me that the big impetus behind the readiness initiative is that a lot of states were feeling sandbagged.

We had come forward with a

recommendation and the implication being any self-respecting state ought to be screening for these things, and so bring it on.

And a lot of states, of course, weren't ready because we weren't sensitive to a lot of the complexities there.

So sort of thinking out loud if we might think about separating our processes a little bit and coming to its termination first about ABC. And if it's an A, then go forward with the Public Health Impact.

And at that point, the states ought to know that the committee has already determined that this is an A.

So it's critical that you give some feedback so that the states understand the, so that the process understands what the barriers are and whether that then, secondarily, is going to be determined from the readiness scale to be a one, two or three.

But that also may give us an opportunity in our recommendations to the

Secretary to address those barriers that have been identified.

A lot of those are going to be state level issues that maybe the federal government won't have a say in.

But maybe we can make some specific recommendations to try to ameliorate some of the challenges that are identified in the public impact portion that might assist states in both participating in the system and recognizing that we're sensitive to the barriers.

And that way, at least, I think we get around to what Charlie said which is a positive recommendation is what makes states get ready.

All right, and in certain circumstances. So if we hold back on some of those recommendations because states aren't ready, then it becomes a circular problem.

CHAIR BOCCHINI: Coleen, were you going to say something similar?

DR. BOYLE: Well, it's kind of a

follow on, on that. And I did, your group here may have already done this and that was to, since we've been talking about the conditions that have been added to the panel and the slower uptake perhaps of the them, I'm trying to get a better sense of what the issues are at the state level in terms of implementation.

Obviously, each commission is going to be different, but there may be some generalizable issues.

CHAIR BOCCHINI: Okay. Let's go to Kellie and then --

(Simultaneous speaking)

DR. KELM: So I think the only, I know, concern that some people would have about at least the idea of Step 1, Step 2, but I think some of the idea was to do them together to try to get the advocates an answer earlier rather than later.

Obviously, if you make it a two-step process then it would be longer for them. I think that's the one thing that we hear about

if we did it two step.

CHAIR BOCCHINI: And it is true. We had this similar discussion the past and decided that they were so entwined that we really needed to get them both started in a reasonable way and that they kind of overlap.

But there certainly is some benefit to the other way, but I think we decided that it would be better to do them together so that one; it would shorten the time line.

And then two, it would, but we need to do a better job in making the states aware of what was going on so that they have more of an in depth opportunity to answer the questions.

And so that's what really evolved from the Pompe decision was that we needed a stronger public health impact analysis, which was based on the states having a better understanding of what the issues were as you mentioned, Jeff.

So, I think Debbie's next.

DR. BADAWI: Well, I'm sensitive to

what I'm hearing also about states. We're trying to separate in some ways the scientific evidence review from the practicalities of putting a new newborn screening program into place.

But I do think it's helpful for states when this committee makes a recommendation because even though it may take several years, let's say, for SCID to be implemented, as Carole can attest to, it's helpful to be able to say this condition has been on the cusp for X number of years.

And it helps us advocate with our legislators to provide what's needed to get that into place.

And the other piece, the comment I had was that if I remember your slide correctly you said that when we look at readiness, we're looking at once funding is available.

So I guess the very basics of having money available to do the test is out of this equation, once funding is available how if all

the stars align, how many are you, or --

(Simultaneous speaking)

DR. KEMPER: Yes, I mean it's like, right. So this is like an important nuance because it's a time, you know, it's so funny.

It's like I'm reliving these conversations and there are like all these branch points where we could've like really gone.

When I say we, I mean you because I'm just the, I'm here to represent the needs of the advisory committee.

So the idea was that if today someone said go out and screen for MPS I, right, and if you had the authorization and not somebody said we'll make the funding available, what would it really take you to do?

So it doesn't necessarily take the money out of the situation because if it turns out that it, that you need to rebuild your entire public health laboratory and get all this new equipment and so forth and the amount of money

to implement the screening test would just outstrip usual sort of funds.

So it doesn't, these are nuances. And I, my understanding of what the advisory committee runs and responds, right, because ultimately I'm happy to do, provide you with whatever information you all need.

But was it just like once the gates are kind of open for you to begin screening for the particular condition.

DR. WATSON: All right, so I have two things where it's actually looking at those barriers a lot more carefully because it's not just to tell you that you got problems.

I think if it's money, then you can be talking to the Secretary about how do you improve Title V so that it's not placing the total burden on the state.

There are ways where you make a federal recommendation, but the feds can actually support the state's ability to address the problem more readily.

If it's training, CDC does a lot of training and new technologies that the state might not be aware of that can speed things up.

If it is a brand new platform, that's another cost issue that has to be factored in, and you all can think about that in the course of your recommendation as to whether the kind of funding needed through Title V or whatever supports newborn screening programs for the states can include those things that allow them to do it.

And it probably means you also have to look at, I mean I've always said there was an odd return on investment problem in newborn screening where the state puts the money into the screening.

The private sector probably wouldn't do it. Many in the private sector realize the benefit by saving on their health plan or whatever it is because of the care of that individual.

And the state saves something on

Medicaid. So I think if you look at it more granularly at the barriers, how do you distribute that kind of a cost fixture because that was one of Secretary Sebelius' big problems was imposing costs on states because there wasn't a system in place to try to address that recommendation that you're putting on the states.

So I do think it's worth looking at the barriers and then thinking more about them because I think you can get to the point where you're almost be able to anticipate how long it should take or a particular condition to move through the process and be approved by the states.

If the legislature is the biggest problem, then you probably tell the newspapers, and that may get them active or not.

DR. KEMPER: I'm going to --

(Simultaneous speaking)

DR. KEMPER: Joe, Dr. Bocchini, I want to go to some other stuff. I'm sensitive

that it's now 20 minutes after 2:00. Can I keep rushing ahead, or how much time can I have?

CHAIR BOCCHINI: Well, let's give, yes, I think we're going to try and truncate it. But Freddie, you have a comment and then we have a comment. And that will end it.

DR. CHEN: Okay. I mean I was just going to say, I don't think there's a state in the Union where the issue is not funding, nor are there any barriers that couldn't be solved by funding.

And so I get what we're trying to get to by saying if the funding were available, but then how do you fix that? And how do you get there?

CHAIR BOCCHINI: I'm sorry. You got a response to Freddie's comment or --

(Simultaneous speaking)

DR. KEMPER: No, well I think money never hurts, right. But I think that, I mean there are some nuances that probably go beyond money. And so was there another question

before I go on.

CHAIR BOCCHINI: Yes. I think the question from the --

(Off microphone comments)

CHAIR BOCCHINI: Okay. Real quick. Okay.

(Off microphone comments)

CHAIR BOCCHINI: So if you could --

DR. KEMPER: So just to wrap up really quickly --

(Simultaneous speaking)

DR. KEMPER: -- that means. Right, so I'm all with you in terms of it would be nice to have better linkage between the people who pay for things and benefits and so forth.

But we got to get MPS I, the Public Health Assessment they are going in. So we've come up with a way that isn't perfect and we're going to learn a lot from it.

It's in the presentation that, I sent Ms. Vasquez this document, and I guess she can, I don't know if she sent it out to you or

not.

I can make sure that it gets sent out to you, where I'm working with the feedback that we got from the meetings that we've had and with others in the condition review workgroup and people outside of there as well to come up with like a list of things.

They could either be barriers or facilitators, depending upon whether or not you had the equipment and the, and so for there, and you can't read any of that.

And I'm not going to go through it right now, but we just asked people to take a look at it. And you can see that, so these are first states that are doing it.

And it will allow us to quickly get at a sense of like what things are hard and what things are not as well as them getting them some free text response.

And then ultimately asking the states as well to put where they see themselves in that matrix of within a year, one to three,

and more than years or just no idea.

So I think that how states perceive things and where they think they fall into the matrix is going to be helpful.

So if you hear from most states that given the information that we provided to them about the screening for the condition that they came to it within three years or they're not even sure, that's one thing versus if we hear back from states saying that they can do it.

So I think it's going to be sort of an interesting question before spinning it into the matrix. And then we get a bunch of other sort of information about the people that are responding.

So again, I knew that this was going to be a hard thing to talk about. I'm confident that we're going to be able to find X, but it's going to take a little while for us to get there.

CHAIR BOCCHINI: I think we're in good hands, Alex.

DR. KEMPER: Okay. I have to say,

we have a good time on our calls, but it's a lot of work.

CHAIR BOCCHINI: All right, well thank you very much. And I think very importantly I know we don't have time to go into detail.

But I think it's very important for everyone to look at this survey and to give feedback.

I think that there are things that everybody can add to this or modify so that Alex, APHL, Jelili have the means to get the information that we need. So Denise.

DR. DOUGHERTY: I did look at it, and along with your suggestion I would say that it could use probably some cognitive testing.

(Off microphone comments)

DR. DOUGHERTY: You're going to do all that? Okay.

(Off microphone comments)

DR. DOUGHERTY: And then, do you have to go to OMB for clearance before you start

interviewing it, not for the cognitive testing but --

(Off microphone comments)

CHAIR BOCCHINI: Okay. All right, any other questions, comments? If not, thank you all for your participation in this afternoon's sessions.

We now have a short break, so we'll give you about a ten minute break. And then the three subcommittees are going to meet. I think Debi, you have the rooms that the break out will occur?

MS. SARKAR: The laboratory, standards and procedures will be in this room. Education and training will be in Room B. The follow up in treatment is in Room A.

CHAIR BOCCHINI: All right, so have good subcommittee meetings. And we'll meet again here as a full group at 9:00 a.m. tomorrow. Thank you all very much.

(Whereupon, the above-entitled matter went off the record at 3:25 p.m.)