SECRETARY'S ADVISORY COMMITTEE ON

HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

Thursday, May 17, 2012

MORNING SESSION

8:30 a.m. — 11:45 a.m.

Hilton Alexandria Old Town Hotel

1767 King Street

Alexandria, Virginia 22314

APPEARANCES

COMMITTEE MEMBERS:

JOSEPH A. BOCCHINI, JR., M.D. - Chairman

DON BAILEY, PH.D., M.Ed

CHARLES HOMER, M.D., M.P.H.

STEPHEN MCDONOUGH, M.D.

DIETRICH MATERN, M.D.

ALEXIS THOMPSON, M.D.

ANDREA WILLIAMSON, B.A.

EX-OFFICIO MEMBERS:

COLEEN BOYLE, PH.D., M.S.

SARA COPELAND, M.D.

DENISE DOUGHERTY, PH.D.

KELLIE KELM, PH.D.

MICHAEL LU, M.D., M.P.H

MELISSA PARISI, M.D.

REPRESENTATIVES

NATASHA BONHOMME, B.A.

FREDERICK CHEN, M.D., M.P.H., FAAFP

REPRESENTATIVES (continued)

JANE GETCHELL, DR.PH., MT (ASCP)
CAROL GREENE, M.D.
CHRISTOPHER KUS, M.D., M.P.H.
NANCY ROSE, M.D.
BETH TARINI, M.D., M.S., FAAP
MICHAEL WATSON, PH.D., FACMG
EMIL WIGODE
MARY WILLIS, M.D., PH.D.

C O N T E N T S

P R O C E E D I N G S

CHAIRMAN BOCCHINI: I'd like to call the meeting to order. Thank you. I want to welcome you all to the 27th meeting of the Secretary's Advisory committee on Heritable Disorders in Newborns and Children, and welcome to Old Town, Alexandria. I think we have a good meeting ahead of us, and we welcome you all to it.

We're going to start off with some administrative business. First is the roll call for the members of the committee. Find out where it is. Got it. Okay. We'll go alphabetically.

Don Bailey?

DR. BAILEY: Present.

CHAIRMAN BOCCHINI: I am here.

(Laughter.)

CHAIRMAN BOCCHINI: This is a very sharp committee. Dr. Botkin is unable to be here today. Coleen Boyle?

DR. BOYLE: Here.

CHAIRMAN BOCCHINI: Sara Copeland?

DR. COPELAND: Here.

CHAIRMAN BOCCHINI: Denise Dougherty?

DR. DOUGHERTY: Here.

CHAIRMAN BOCCHINI: Alan Guttmacher is not here today.

Kellie Kelm?

DR. KELM: Here.

CHAIRMAN BOCCHINI: Fred Lorey will call in if possible during the day. Michael Lu is not here yet. Stephen McDonough?

DR. MCDONOUGH: Here.

CHAIRMAN BOCCHINI: Dietrich Matern? And then I have Melissa as down on the list here.

DR. PARISI: I'm here.

CHAIRMAN BOCCHINI: Alexis Thompson is not here.

And then Catherine Wicklund is unable to be here today. And Andrea Williams.

MS. WILLIAMS: I am here.

CHAIRMAN BOCCHINI: All right, thank you. And then representative members in attendance, I know Freddie Chen is to call in. Is Freddie on the line?

(No response.)

CHAIRMAN BOCCHINI: Not yet? Okay. Beth Tarini, American Academy of Pediatrics.

DR. TARINI: Here.

CHAIRMAN BOCCHINI: Michael Watson from the American College of Medical Genetics.

DR. WATSON: Here.

CHAIRMAN BOCCHINI: Nancy Rose representing the American College of Obstetricians and Gynecologists.

DR. ROSE: Here.

CHAIRMAN BOCCHINI: Jane Getchell, Association for Public Health Laboratories, not here yet.

Chris Kus, Association of State and Territorial Health Officials.

DR. KUS: Here.

CHAIRMAN BOCCHINI: Bennett Lavenstein, Child Neurology Society?

(No response.)

CHAIRMAN BOCCHINI: Mary Willis, Department of Defense?

DR. WILLIS: Here.

CHAIRMAN BOCCHINI: Natasha Bonhomme, Genetic Alliance.

MS. BONHOMME: Here.

CHAIRMAN BOCCHINI: Emil Wigode, March of Dimes?

DR. WIGODE: Here.

CHAIRMAN BOCCHINI: And Carol Greene, Society for Inherited and Metabolic Disorders.

DR. GREENE: Here.

CHAIRMAN BOCCHINI: And that's the roll call.

DR. COPELAND: Thank you, guys, all for coming today. It doesn't look like it yet this morning, but the prediction -- the forecast for the weather in the room is such that you will have to be nice and close to each other because we've had an unprecedented number of sign ups. So the people in the audience is whom I'm speaking to. So feel free to get to know your neighbors. Your purse doesn't get a seat, all that other good stuff. Obviously while there's still empty seats it's not an issue,

but as people come in, please be friendly.

Another issue is microphones. In order to speak, you have to turn on your microphone, and if you don't want everybody else to hear you -- what you're saying, you know, to your neighbor afterwards, you need to turn it back off.

And then, let's see, restrooms. When exiting the General Session, the restrooms are down the hallway to the left. The Altarum staff will be at the registration desk for any questions.

Subcommittees will be held 2:00 to 5:00. The Lab Standards and Procedures is in the Madison Room, which is on the second floor. Treatment will be in here, and Education and Training is in the Washington/Jefferson room on the second floor. And if any of the presenters have changed their presentations after submitting them, please provide a revised copy of your presentation.

And you should've received a thumb drive, which is in front of you, that has the supplementary material. I didn't think there could be more than 800 pages, but anyway, thank you.

Oh, yes, everybody turn off your phones, or at least turn off the ringers, just as a reminder.

CHAIRMAN BOCCHINI: Thank you, Sara.

The first item of business is approval of the minutes from the January 2012 meeting. Are there any additions or corrections to be made to the minutes that were sent with the book?

(No response.)

CHAIRMAN BOCCHINI: Hearing none, I will ask you to approve the minutes. All those in favor?

(A chorus of ayes.)

CHAIRMAN BOCCHINI: Thank you.

Next is just committee correspondence and correspondence to the secretary as a result of the recommendations of the committee from the last meeting.

And then now we'll go to Sara, who is going to discuss organizations' representative categories, the annual report, the reauthorization report, policies and procedures, and provide us with updates in those areas.

DR. COPELAND: Thank you. Good morning again. My slides will be popping up. I just wanted to give you guys an update after the last meeting what changes we've made and where things stand. So we'll talk about updates, review the org reps, and some of the changes to subcommittee procedures and processes, and then an update to the condition nominations. We thought we would streamline some of the nominations.

So the Newborn Screening Saves Lives Act reauthorization is due in 2013. So far no action has been taken. However, the nice thing is it doesn't go away. It does not sunset so long as funds are appropriated.

The 2012 annual report was reviewed and approved by the Advisory committee and has been sent to the Secretary. And to further elaborate on the organizational reps, we fleshed out a little bit about what we will be asking the nominations maybe provided to myself from organizations, and perspective and expertise provided by the nominated representatives, and why this perspective and

expertise would benefit the committee, and have the committee's work affects and/or impacts a nominated representative's organizations and stakeholders and the commitment of the nominated representative to provide expert input into the process. And a source of funding and a means for ensuring active dissemination to their representatives about the committee's activities.

Since I happen to have had my slides turned in for approval, this last bullet is incorrect. It's actually the nominations will be viewed by the Chair and the DFO, and then you will vote on them. It means it will take less than two years to get appointed.

Just so you know, these are the organizational representatives, their categories in the rotation. You saw the terms. We have a number of representatives there right now for the organizational meeting. And if you will look at the representatives, these are the categories, but we have one vacancy there. The Association of Public Health Laboratories will be rolling off, and we can

have more turnover for different groups. And as you can see, the Association of Public Health Labs will begin in January of 2013. And the American Academy of Family Physicians, et cetera, will be releasing an FRN and a request for applications to the public.

But we do have a public health constituency. In my effort to get everybody to fall into my nice little box, we have tried to make reports of projects and forward to the Advisory committee a little bit more structured for any projects, for reports coming out of the subcommittees. The request is first off the nature of this board meeting requested, what we'll be voting on in January. And if the project or the work of the actions of the Secretary, they need to very clearly state what actions, the recommendations are.

Please list the pros and cons of each action and/or recommendation for discussion by the Advisory committee and what is the best mechanism for the Secretary to support these actions.

So to simplify it for the Advisory

committee, we will have a voting slide which will have the title, the nature of support requested, and if there are actions, the pros and cons of each action and recommendation. For the condition nomination form informally in the nomination, we kind of have a couple of things considered fatal flaws, that if they haven't done, they will go forward to the nomination and prioritization. And instead of having to cast those or try and figure out what those are, there's three or four requirements: a population based pilot, a validation of the laboratory test, and a widely available confirmatory testing with a sensitive and specific diagnostic test.

So the nomination condition form is even more complicated now when you look at it. I've added another table at the top. But hopefully this will help for the nominators so they know what we're really looking for, some of the things that are really important as we move it forward.

After discussion with Don Bailey, our education expert, we are going to try and come up

with a layperson's explanation of the form and what's being requested. But at this point in time, we don't have it. But these are the issues that are -- that we're looking at. The population-based pilot, and just kind of breaking it down -- location, number screened, number positive, and number confirmed, if you have validation information, and the confirmatory testing.

And that is it for the updates. Any questions or comments?

CHAIRMAN BOCCHINI: Kelly.

DR. KELM: I'm sorry. Can we provide comments on the last form?

DR. COPELAND: Yes, definitely.

CHAIRMAN BOCCHINI: Steven?

DR. MCDONOUGH: I have a question. Do you have any timetable for linking the birth certificate on the newborn blood spot on the interim?

CHAIRMAN BOCCHINI: Well, that was sent to the Secretary, as you saw, as a recommendation to make States aware of the various opportunities they have to improve the linkage between the birth

certificate and the laboratory results. But it is now in the Secretary's hand, and it was just a recommendation to do that. So we don't know what she will do with the timetable.

DR. COPELAND: She has up to 120 days to respond.

CHAIRMAN BOCCHINI: She has 180 days to respond. Okay, so there we are. Okay. But we do know. Other questions or comments?

I think it's very clear that some of these changes really improve the structure of the way the committee operates, and then by providing a timetable for the terms for individual liaisons to be on the committee organizations. It allows for a greater opportunity for people to participate at the liaison table, and I think that will strengthen the work of the committee as well. So I think those seem to be moving forward in a very nice way. So thank you.

Don?

DR. BAILEY: So, Sara, did you say when the call for nominations will be coming out for the

next round of organizational reps?

DR. COPELAND: In the next couple of weeks.

DR. BAILEY: Next several weeks, that soon.

CHAIRMAN BOCCHINI: Other questions or comments? All right, thank you.

So the next item on the agenda, subcommittee priorities and projects. And this is here because we have -- at the last meeting or last couple of meetings, we've talked about how the subcommittees are operating and the number of projects that they've been involved in. And our goal is to try and focus the subcommittees to prioritize their work, but do that with input from the committee so that ultimately the things that come through the subcommittee will really be ultimately prioritized and be focused by the entire committee.

So in this part, we want to kind of review where each of the subcommittees is and see where their priorities are to sort of inform the committee

in general, then get some feedback from the committee. This will be part of the discussion in each of the subcommittees today. And then we'll come back tomorrow and see about focusing further the work of the subcommittees by the general committee.

So first, Don, Subcommittee on Education and Training.

DR. BAILEY: I can't talk without slats.

(Laughter.)

CHAIRMAN BOCCHINI: We all understand that.

DR. BAILEY: Great. So the Education and Training committee has, as I've said before, a very broad charge. We are to review existing educational and training resources, identify gaps, and make recommendations with regard to the entire universe. So parents, and the public, and health professionals, including physicians, screening program staff, and hospital birthing facility staff. So we think actually this is a good time, Joe, and we like the idea of trying to prioritize and focus

our efforts because that's what we need to do.

So we've been told to limit it to three priorities. And so our first priority is to continue to track, provide input on, and facilitate the integration of national initiatives as well as committee-initiated activities. And so in this context, we have, as you know, on our subcommittee representatives from a number of the major professional organizations and other kinds of groups -- pediatrics, OBs, family physicians, the Department of Defense, March of Dimes, the various regional collaboratives. And so in each of our meetings, they provide updates to us on what their organization is doing with regard to newborn screening. And we'll try to be more intentional about asking those groups to ask to find out what they need from us as a committee, and then us as a subcommittee reaching back to them and making some recommendation for next steps. Obviously this committee can't tackle everything, and so we really rely on these organizations to do this.

Also we'll keep tracking major education

and awareness activities. A number of these were stimulated by our subcommittee in previous years. And so these would include examples like the Genetics and Primary Initiative, the Newborn Screening Clearinghouse, and other major sources of information for the public and professionals.

We're also adding to this priority to continue to track research and policy developments that might impact the subcommittee's activities or recommendations. And so, for example, we were approached by a couple of people recently to meet with the committee and share research that they've been doing on State laws and how they affect actual practice and participation in dry blood spot retention and use programs.

This clearly is under the purview of the larger committee. We did have a report to the Secretary on recommending some things that the State should be doing, and we think our committee would be in a good position to track what's happening nationally.

So there'll be issues like this. There'll

be things on new developments and developing materials for the public or different ways of communicating with the public. And so we'll try to include a research spotlight in each of our sessions going forward as well.

So our second priority is, again, a broad one, but is to continue to promote newborn screening awareness among both the public and professionals. And so as I reported last time, in 2013 there will be a major newborn screening awareness campaign that HRSA is providing input on, and it will be then coordinated by the CDC and APHL.

We had a strategy meeting, summit a couple of weeks ago to help provide input on that, and we'll be discussing that in our subcommittee, and I'll report further details of that in my report tomorrow.

But our goal as a committee is really to help -- continue to think about ways to provide public awareness and to really capture and take advantage of the 2013 50-year celebration, again, which we'll talk about tomorrow.

But we want to make sure that we don't limit our work to one year, have a big celebration and then all walk away from it. It's not going to permanently change things. People are still going to be having babies, and babies are going to continue to be screened. We need to have a more institutionalized set of practices for promoting ongoing awareness and support for newborn screening after the big party.

So we view this as a long-term set of priorities for our subcommittee and working in tandem with the various professional organizations, and the hospitals, to see what we can do to help facilitate that.

And our final priority -- and you alluded to this, Sara, already with the nomination form, is to continue to take on this task of providing better guidance for advocacy groups and others regarding the nomination and review process. Alex Kemper from the Evidence Review Group will be joining us in our meeting this afternoon. And we'll be talking about the Education and Training Subcommittee can

collaborate with the Evidence Review Group to make this possible.

We think the work that you've done to improve the nomination form will be very helpful. But we'd like it to be really clear to all the advocacy groups, you know, here's why we have certain criteria in place, and here's what you can do to get your condition ready for nomination review so that we're not just a we'll wait and you bring it, and then we'll decide, but to help facilitate that process more.

So our goal over the next year is to work with the Evidence Review committee and to come back with the -- to the Secretary's Advisory committee to talk about strategies for achieving both of these goals.

So those are the three primary priorities for the Education and Training committee that we'll be discussing today. And I assume we'll be coming back tomorrow then with an edited, updated version of these for committee review.

CHAIRMAN BOCCHINI: Yes, thank you. And

included will be some of the specific projects that you might be considering, so perfect. Denise?

DR. DOUGHERTY: So is this the time to discuss -- okay. So I guess one thing that troubles me a little bit is the focus that seems to still be there on promoting newborn screening. And I guess we might want to go toward a more balanced view. There are some issues in newborn screening that parents are concerned about, like informed consent and so forth. And acting as if they don't exist and promoting newborn screening as if it were all good all the time for every person, you know, it is 99.9 percent good. But to not acknowledge that there are some challenges and issues and be forthright about how to deal with them I think would be a mistake.

DR. BAILEY: Well, I couldn't agree with you more. I think the future will only become more complicated in those topics. And issues regarding consent and the disclosure of carrier status or conditions for which there's uncertain outcomes, and treatments that may only be partially helpful or may, in some cases, be harmful are complicated

issues. And we do think that that's a part of our subcommittee's responsibility and this committee's responsibility to make sure that we don't just out there -- well, we are champions for newborn screening as an endeavor, and that's certainly a part of our task. But helping the public to deal with the nuances of all these complicated issues is incredibly important. So I fully agree with your comment.

DR. BOYLE: Well, first I wanted to applaud you on just great, I think, terrific objectives. I think they're really at the high level and a real clarity. I particularly like the third one on really trying to help facilitate this process for people who are trying to move forward on it. So it feels like a new one for you, so I thought it's just a terrific idea.

And on the second one, while I agree with what Denise said in that discussion there, remembering back to how this issue came to the committee a couple of years ago. The thought really was to try to demysticize newborn screening and

create a demand for it, you know, sort of an educated demand. And not so much the education and awareness piece, but getting the general public to recognize that this is something that they would anticipate, expect, and, you know, they wouldn't walk away from having a child without recognizing that all those things fell into place, just like with immunizations.

So it's a little bit of a different focus from my perspective, so, I mean, it's just an issue to consider in your subcommittee discussions.

DR. BAILEY: So I don't know if there's a specific response needed, but I do think that -- so you're saying it's more than just awareness that we're trying to promote. It's education and it's -- I don't know if we would call it marketing, but it's definitely helping families see that this is something that is going to happen, and it has -- and you should be looking for it. You should be asking for it. You should be asking what the results are.

DR. MATERN: I appreciate that we want to promote newborn screening. Fred is not here, but he

might say there are some people that don't need to be educated about promotion, but actually to take it back a little bit and not just go forward and push it through. How do we reach those people and educate them? So State legislators, support groups, and so on.

DR. BAILEY: All right. So I think that's a major goal of our third activity, more public understanding of the process, and not only what the steps are, but the rationale for those steps so that we can still have a rational approach to making decisions about expansions of newborn screening.

So I think what we're doing is in line with what you're talking about, but we'd like to hear more if you have some further comments.

DR. MATERN: Well, I wonder in particular when it comes to California where they now are supposed to screen for Krabbe disease, which this group decided is not ready for prime time. And yet you have a patient support group that feels it is prime time, and then just goes to one legislator after the other, and basically he pushes it through,

comes up with weird deals where they scale back from five disorders to two, and just pick out one out of the hat, you add a second one.

What can we do to make legislators aware of what this committee is doing and why they decided that it's not prime time?

DR. BAILEY: So that's a complicated challenge, both political, and scientific, and communication. And so, you know, I think at one level our committee can kind of take a higher road view of -- not higher road, but take the high view and say, yeah, our job is to set the standards. And we can't really control what goes on in the different stage with regard to things that you just described, but we can continue to provide.

But I do think appropriate information for legislators could be a potential audience for us as long as we're not engaged in lobbying and those kinds of things. But I do think we could certainly think about that in terms of appropriate materials and so forth.

I don't know, Joe, you might have -- Dr.

Bocchini, you might have a comment on what --

CHAIRMAN BOCCHINI: You know, I think it's a good discussion, and I think that the committee in its decisions and deliberations can certainly serve as a resource to State public health organizations when these come up in the legislature to provide background materials or other information that would help inform the legislators as those things are being discussed about what the science is and why the decision was made, and that, in fact, a decision was made by this committee. And that might help inform a State legislator about whether to go forward or not.

So I think we certainly can take an active role and be a resource for the States under those circumstances.

All right. Additional comments on this question?

DR. HOMER: Yeah. Just building on that. On that your first slide here, you did say the world. I did reflect that actually legislative policymakers were not on your list, and there are

both through public health, but, you know, National Governance Association, National Council of State Legislatures. I mean, there certainly are other policymakers that we could specifically develop briefing books, briefing materials for, for example, that might be helpful.

DR. BAILEY: All right. So collaborating through some of these major organizations rather than on a State by State basis. Maybe through the National Council on State Legislatures or something like that would be a good strategy for us.

CHAIRMAN BOCCHINI: Natasha?

MS. BONHOMME: Great, thank you. My question had to do with the 2013 campaign and beyond that. So, you know, that's a really big effort that's underway, which is really great, by the CDC and other partners. Do you see the role of the subcommittee after that being picking up the baton, or continuing to provide input to whichever agency or organization decides to continue after 2013?

DR. BAILEY: Yes.

(Laughter.)

DR. BAILEY: So the committee doesn't -- I mean, we really don't have resources to, you know, develop things and do new activities, but I do think that we will have an ongoing responsibility for this overall objective beyond the 2013 campaign. And so this will be one of our tasks in our subcommittee meeting this afternoon, which is to start thinking about more specifically what could those actually be.

CHAIRMAN BOCCHINI: Thank you. Carol?

DR. GREENE: Thank you. And very briefly regarding number 2, I think perhaps if you link back to the whole theme of Medical Home, that perhaps one of the elements that you're looking for in education is for families to be informed and active participants. And that could go to what Denise was mentioning that, you know, families have a right in some places to say no to some things, like research and understanding what are their roles. So it's more than just awareness. It's an active involvement and understanding of the whole process.

My question is much, much, much, much

bigger. I think those are terrific objectives, and this is a question probably for the whole committee to consider in terms of what the Education Subcommittee will be doing. There is a boatload of stuff to be done with newborn screening, but all three of your main goals are very newborn screening focused.

And I think that we are -- I think that we will do better by newborn screening if we don't remain completely newborn screening -- solely newborn screening focused. But also that I think I would like to see some discussion in the larger committee about -- there's a sense that you have to be on the newborn screening in order to get any care or attention, and there are some things like Krabbe that don't belong on the newborn screen, but we still have responsibility to those babies, not to mention Downs syndrome and neurofibromatosis. And just having people understand that genetic disease is important in Medical Home.

And I would like to see some discussion from the education side of genetic, inheritable

diseases in general, not -- and to be clear, I don't think that the role of this committee would be to tackle all of special needs. There's lot of special needs information support from wonderful support groups focused on the genetics. But newborn screening isn't all of genetics.

DR. BAILEY: So I would certainly agree with you, and we're not the Secretary's Advisory Committee on Newborn Screening. We're the Advisory Committee on Heritable Disorders in Newborns and Children. So this is a broader committee discussion. Our subcommittee would be grateful for some input from the broader committee on what might be some priorities.

The genetics and primary care initiative would be an example of one of those things that goes beyond newborn screening. But you're right, most of what we're doing right now is newborn screening.

DR. MCDONOUGH: Yes. I'd like to just thank you for bringing up those comments. As a pediatrician in practice, I can tell you that most of the kids with genetic diseases I see are not

picked up in the newborn period. And there's big gaps out there in care and resources for them. Hopefully within the next few years we're going to be able to incorporate more discussion about some of those needs that need to be addressed.

DR. KUS: Yeah, a comment and a question. I think the discussion about legislative involvement with this, I think the idea of having an awareness for national legislative offices and things that -- there is a process for going because most of the time they don't have a clue that that's what's happening, and then they're responding. So that's one point.

And I guess the question I have for you, Don, is the committee going to develop a strategy for ongoing promoting, recommended strategy for ongoing promotion of the awareness of newborn screening so that we do have an educated population? Do you see that as a --

DR. BAILEY: We see that as an aspirational goal, yes. You know, it's going to involve many different entities. Certainly OBs will

be key to that in terms of prenatal on education, the hospital and birthing facilities, pediatricians when they have follow-up discussions with parents.

And so there's the education and awareness for parents -- for new parents and potential parents. But the public at large, if that's what you're asking about, is a much bigger kind of issue, and I think we'll focus first on new parents as our primary awareness target.

But I think you're right. The factual information for State legislators -- in fact this committee exists and the process and the decisions we make is important.

DR. TARINI: As the co-chair of the Education Committee, I want to applaud Don and Sara for having thoughtful discussion and decisions around the membership of this committee moving forward such that these comments and questions about multidisciplinary educational efforts are going to be more easily addressed now as far as I see it on this committee by having members coming from different stakeholder groups. It really diversifies

both the input and the ability to leverage resources.

DR. BAILEY: Thanks for mentioning that, Beth. And in my report tomorrow I'll describe our new committee members and the process, which I thought worked great.

CHAIRMAN BOCCHINI: All right, thank you very much. It's very clear that you're well on your way to a very organized approach.

DR. BAILEY: I thought there wouldn't be any discussion to this.

(Laughter.)

CHAIRMAN BOCCHINI: I think the discussion was very good. I think it helped bring out additional points very nicely. So thank you.

Next is the Subcommittee on Laboratory Standards and Procedures. And in Fred's absence today, Sara will provide that report.

DR. COPELAND: Thanks. Today is a case of do I say, not as I do. I asked the subcommittees to come up with three priorities, and this was kind of a last minute me covering for Fred. So I don't have

the three priorities.

So there's a list of things that we discussed, and hopefully we'll be able to integrate more. And then we will have only three priorities tomorrow morning, I promise.

So last September, as Joe mentioned, we had a discussion of the different things that the Lab Standards and Procedures Subcommittee has done. And some of the main issues that we think are important for our subcommittee is reviewing new, enabling, and disruptive technologies, and help to provide guidance for States making decisions about the implementation of new screening tests, provide the data and the information that is kind of unique to the subcommittee in that we can -- we, not me, Dr. Matern in particular has a comparative performance metrics information. And we can provide the technological background for the overview of new technologies.

Discussion of point of origin or point of care, testing versus traditional newborn screening labs, how this can be integrated into the States.

And establish a process for regular review and revision of the standards panel, maybe remove disorders, who knows? Alter the status for secondary to primary targets. So looking at the recommended uniform screening panel and how we can provide some ongoing feedback on that.

And then when changes in technology come up, how to best guide States and provide the information to States on how -- on the information regarding metrics versus -- classic example is tyrosinemia type 1. Initially the screening for tyrosene, but lessons learned is that succinylacetone is probably the only real good mechanism for screening for tyrosinemia type 1. And how can we best provide that kind of guidance to the States?

Continued activity for HIT standards and the workgroup there, as well as monitoring new technologies.

And harkening back to our last discussion, we probably do need to start looking more and more at the heritable disorders, not just newborn

screening, and how this can -- how this subcommittee can help the Advisory Committee with their work.

So that's it. We will be much more organized tomorrow, I promise. But we can -- if you have suggestions, that would be useful.

CHAIRMAN BOCCHINI: Carol?

DR. GREENE: It seems like a great moment for me to mention something that I think this committee, and this would be the right subcommittee, but the committee could help a great deal with, and that is the enormous opportunity, and I think some incredible challenges coming with the NIH genetic testing registry, and especially in the biochemical community. People have engaged in the -- and I want to say for the record, the GTR folks have been absolutely willing to talk and explore how to improve things. But it's very clear that biochemical tests do not fit into the GTR. And I think there's some other questions about how people can use the GTR and understand the GTR.

And I think that it does go beyond newborn screening, but for starters, how would you put a

newborn -- you know, how would you put newborn screening as a test into the GTR? It's complicated.

And the GTR is absolutely wiling to engage, but they need people to engage with. And I think that would be an important activity for this subcommittee and for the whole committee.

CHAIRMAN BOCCHINI: Thank you. Other comments, questions? Natasha?

MS. BONHOMME: Hi. Has the Laboratory Committee -- I know this is very specific in terms of being in the lab. Has the Laboratory Committee discussed issues around conditions being added to States panels that they feel aren't ready for prime time, back to the comment before? I'm just trying to think of, if that conversation has happened in the Laboratory Committee.

DR. COPELAND: No, we haven't really brought that up, but that is a good point. And something that we should consider as well is how can we best support the States that are in that position?

MS. BONHOMME: Because I think that would

be helpful as a member of the Education and Training Subcommittee just to be able to hear more concretely about perspective and then to see how that can be integrated throughout all the subcommittees and then at this level here. Thanks.

CHAIRMAN BOCCHINI: Carol?

DR. GREENE: Under the heading of new, enabling, and disrupting technologies, we've got whole genome sequencing, and it's moving very, very, very, very, very, very fast, and I think it needs to be considered.

DR. COPELAND: What about it? I mean, what would the -- what do you see the role of the Lab Standards and Procedures?

DR. GREENE: In this case, I think I would -- I personally would stay newborn screening focused on that particular question, because there are a number of groups, including ACMG and a whole lot of other folks, who have gotten together to try to figure out some of the important questions there, like how do you handle reporting incidental findings. And I would not look at the whole world

there.

I think I would say how is whole genome sequencing going to -- because we're getting to a point where people are going to bring the cost of whole genome sequencing down to the cost of newborn screen. It's already -- the problem is in the information handling. And there are going to be proposals to say, you know, forget all this biochemical stuff; let's just do the DNA. And that's wrong because the biochemical is still the gold standard, and that's the screening standard.

So I would stay newborn screening focused on that one and say how does whole genome technology impact newborn screening.

CHAIRMAN BOCCHINI: Steve?

DR. MCDONOUGH: Has the committee ever invited world renowned experts to give us the perspective on what they see the future for genetics and children, like giving a 10- or 15-minute presentation here?

I mean, the director of the National Institutes of Health is a geneticist, and as a

general pediatrician, I'm very interested in what the impact of whole genome sequencing and the complexity of that with primary care, and then newborn screening labs. Has the committee ever done that, extended an invitation to get more people's perspectives on what the future is in the next 10 years or no? I'd be interested myself in that.

CHAIRMAN BOCCHINI: I don't know if the committee has done that in the past, but certainly I think that's a very -- that's a great suggestion. And I think having the opportunity to bring in leaders in various areas to inform the committee of what's going on and what they see happening would certainly be very informative for the committee and help the committee in its work. So I think that's a good suggestion.

DR. MCDONOUGH: I don't know how the process would be in place with the other committees to support that. But I certainly would be supportive of you extending the invitation. Not something huge because we have limited time here, but I would find that very helpful.

CHAIRMAN BOCCHINI: We have a variety of different updates over time, that there is committee meetings would certainly fit in, and something we certainly can look at as a possible way to do it. Good. All right. Other questions or comments? All right, thank you.

Now the third is the Subcommittee on Follow-up and Treatment. And Coleen has this presentation. Now just I think Coleen, this is your last presentation as the Chair of this committee.

DR. BOYLE: It is.

CHAIRMAN BOCCHINI: And I think we certainly wanted to recognize your work on this committee and all the contributions you've made. And thank you very much publicly for everything you've done.

(Applause.)

DR. BOYLE: And it is a bittersweet parting, but more sweet than bitter I have to say.

(Laughter.)

DR. BOYLE: So just to remind everybody, this is our charge, and I just took it word for

word. Actually I took it from the minutes from the September 25th meeting, so hopefully this is accurate, and reminding everybody that it really is -- all of our charge really relates to newborn screening following the discussion we had earlier about genetic disorders, et cetera. I mean, that could be something we expand our charge to. But right now we are focused on newborn screening.

So the charge itself really tries to focus on identifying barriers to post-screening implementation, as well as short- and long-term follow-up. The majority of the work of the committee really had been focused more on long-term follow-up. Obviously we've had a few activities along the way. The blood spot newborn -- excuse me, vital records linkage is a nice example of short-term -- well, also obviously related to long-term follow-up as well.

So once we have identified barriers, we obviously want to take it to the next level, which is to really think about recommendations that might overcome those barriers. And that subcommittee felt

very committed to adding the issues around treatment. We haven't done a lot of focus other than the medical foods associated with treatment. And medical foods is very important, but thinking more broadly. And then finally offer guidance on responsibility for post-screening implementation and follow-up. And, again, the committee has done some work. I think we can do some additional work in that regard as well.

I just wanted to acknowledge the absolutely wonderful people that I have had the opportunity to get to know and work with. These are just outstanding people, both the subcommittee members as well as the other experts who have really tirelessly provided guidance and advice. And I specifically want to mention Jill Shuger, who has made my life and the subcommittee's life so much easier in terms of her excellent support of the subcommittee work.

So with the three priorities, they really do track back to the priorities that -- essentially the charge of the subcommittee. So the first one is

really to -- and this is sort of broad and I'm going to go into a little bit more depth here. Facilitating screening program implementation and follow-up. The second one is really closing gap and access to care and services. And the third one is, again, in a broad way, improving clinical outcomes.

So for the first one, which is facilitating screening program implementation follow-up, through the work of the subcommittee, as well as conditions that have already been included in the rush -- the panel, the recommended panel, we feel like there are some really good case studies or projects that the subcommittee could embark on. The first one was of one that was of discussion last time for the full committee as well as some more in-depth discussion in our subcommittee, which is really to evaluate the ongoing implementation of screening for critical congenital heart disease. Obviously when a condition makes its way onto the recommended panel, we want to make sure that the committee plays an active role and how that is applied at the State and the hospital level. So,

again, trying to sort out how the subcommittee and the full committee can really help with the ongoing evaluation of new conditions added. So CCHD is really an example of that.

The second example we had in here is hearing screening follow-up. Now to me, this is an example of a condition that's been on the panel where there are complexities. It's another point of care testing condition or a screening. And there have been challenges as we all recognize in terms of follow-up for hearing/screening. So what can the committee do -- subcommittee can do to maybe help facilitate that follow-up? So, again, that's another case study, another project to really help facilitate post-screening implementation.

And then the third one is perhaps a little bit broader. Again, trying to take a higher view on this one, is really this idea of connecting point of care testing with dry blood spot screening both from a public health perspective as well as from a Medical Home clinical perspective. And, again, from a more general sense, what can the subcommittee and

by the way of the committee actually do to help facilitate those very different paradigms? So that's bundle number one.

The second one is really trying to close gaps in access to care. The committee has done work actually when we first started as a subcommittee, trying to recognize and sort of understanding the evolving roles of the various players in newborn screening, thinking of it as a system, and particularly in terms of post-screening implementation.

And we sort of put that aside, got busy on other things. But I think the subcommittee really does feel that it did some really good work. We didn't bring it to fruition, and it might be a good time to revisit that given the changing healthcare paradigm that we're in, and the fact that we have very different conditions on the newborn screening panel now. So really trying to recommend clear guidance on rules. Again, trying to take that higher level of this.

And I put the second bullet in there, and

that's really to try to ground us on understanding both the opportunities -- I always want to put opportunities first -- as well as challenges in the changing healthcare environment. So trying to ground us in that and understand. You know, we're a little removed here as a committee from what actually happens in real world implementation, so trying to make that connection as often as we can.

The final one is improving clinical outcomes. Obviously the reason we screen is to improve clinical outcomes in children beyond what we have done based on clinical identification. And I think this is really a moving target. And, again, this is the same point all over again given the challenges in the evolving technology we can identify. And I think this is the grounding that the committee and subcommittee started with six or seven years ago when I first became involved. Evolving technology and how that influences the healthcare system, and how those two are not necessarily in sync.

So we thought that taking an example, such

as sickle cell, as a condition that might really serve as a test case, to really understand the gaps between the technology, and the ability to identify the condition early, and then the disease management practices. And I took this quote from our notes -- subcommittee notes in September, which was really that we have outstanding interventions, but a very frustrated system of long-term care. So it's really trying to understand how we can help facilitate, and using sickle cell as an opportunity there.

Other issue around sickle cell, and, again, this is why we thought it might be a good test case because it brings in other complexities, including the fact that we can identify trait, and there's variability across States in terms of notification and follow-up, and really how, I think the discussion about genetics in children, and genetics as it relates to a family, as an important issue. And so I think this is a nice example of that.

So I can't remember what the last thing was. Oh, so consider other options. So again

trying to take a higher level view. Sometimes we get down into the condition where a condition can serve as a test case, but really considering other options for overarching approaches that might help provide guidance either to follow up post-screening for the conditions that are already included in the panel, or for those to come in the future that have different complexities.

That's it.

CHAIRMAN BOCCHINI: Thank you for the report. Was there discussion in your subcommittee on the model of childhood oncology, centers collaborating together, looking at data, follow-up, for dealing with the rare conditions, but sort of resources existing to support that process? Is that model something that different tertiary care, genetic, metabolic centers across the country are looking toward collaborating, or it's not appropriate? Is there any discussion on that at all?

DR. BOYLE: So over the years there has been. Actually that case in point has been brought

up as an opportunity and a way to get additional information.

I think what NIH -- or at least that's how I view NIH's funding is that opportunity. And I don't know if Melissa or Mike want to speak up to what you are actually funding, because I guess I think of that as an opportunity for collaboration for rare disorders.

DR. WATSON: Yes, we're doing that.

(Laughter.)

DR. WATSON: And we were in the -- we've gone from sort of the development phase that was two and a half years or so, and we're in implementation. You know, and one of the grantees, there are -- I think we met yesterday actually, somewhere in the neighborhood of 15 institutions in the country are participating. No, I'm sorry, 21 institutions in about 13 to 15 States are already aggregating their data about kids, identify the newborn screening to better understand clinical histories. Beginning to look at candidate conditions in some of the grantees to develop the evidence basis that might make your

life easier when you have to make decisions about whether or not a condition ought to be added to the panels or not.

It's a large task, and we're building the infrastructure, which is a lot of IT and informatics to support the ability of researchers to do this at much lower expense by having centralized core kind of resources that allow that kind of research to take place.

DR. PARISI: Yeah. And I just wanted to add that the Newborn Screening Translational Research Network that Mike is referring to is really trying to develop tools to facilitate long-term follow-up, at least with regard to being able to track individuals and their care, and do it in a systematic manner that can also coordinate with the electric medical records as well.

DR. KUS: Yeah. Just to mention that, I mean, several States have grants for long-term follow-up, and part of the idea is to connect that information, collect consistent information. You also mentioned the cancer. One of the models that

we look at are cystic fibrosis as it's moving into newborns screening because they've collected data on a national level that's to improve care, so that's something we're working with, too.

CHAIRMAN BOCCHINI: Sara, then Don, and then Denise.

DR. COPELAND: As you guys are going forward, especially with the role and responsibilities, CLSI has a very good document on short-term follow-up responsibilities. And we really want to make sure that we are not replicating anything that's been done.

DR. BOYLE: Yeah. And actually ours really did focus on long-term.

DR. COPELAND: It did in the past, and I just wanted to make sure. Yes, and also any work you do with sickle cell needs to be in coordination with the national sickle cell initiative that the Secretary is doing because we don’t want to have an advisory committee to the Secretary and the Secretary's group doing the same thing. It doesn't look very coordinated.

DR. DOUGHERTY: Well, this is great, and I agree with all the new priorities. It's terrific.

I would like to suggest a name change for the committee, though. I think as the committee has evolved and sharpened its focus, and as the world around us has evolved, there's now what's called a focus on quality improvement, including the in the public health world, which is relatively new. Healthcare is a little bit older. But so calling the Subcommittee on Public Health and Healthcare Quality Improvement I think would really capture what this committee is trying to do.

The other thing is that I think the committee -- subcommittee and the committee perhaps needs a little more focus on monitoring and tracking the progress made on its recommendations and activities. So I think we've done a lot of documents, had a lot of recommendations. We haven't quite figured out where to get the data, you know, to say where are we now on those recommendations that we've made. Where are we now in the quality and access to healthcare and long-term follow-up?

So I think that would be a good addition.

DR. BOYLE: So I'm just going to respond. I think the name change, maybe we can take that under advisement on the subcommittee level. I think that's --

DR. COPELAND: It would also require Secretarial review and approval.

DR. BOYLE: Yeah. And then the other issue, I think your point on trying to understand our impact is a great one. So I think that some reflection on that is important because I do feel like at times that we're just producing products which we feel good about, adding to our CVs. But, you know, are we really having an impact?

DR. COPELAND: And that actually is already underway. We've started thinking about how we could do that for the whole advisory committee, not just the subcommittee. So hopefully we'll have a report for you guys.

DR. BAILEY: And so a couple of comments. So, one, follow-up in treatment is almost a definition of screen positive children, children who

have a problem. And so -- but I think there are clearly family ramifications for identification, both of a sick child, but also his carrier status. So I think attention to the family, consequences of diagnosis would be an important piece of the picture for your committee.

And, secondly, again related to the fact that it's all right now all about identified children. And maybe this is too specific a question, and maybe it's known. But do pediatricians routinely inform families that the screening was normal? This would be an opportunity to -- if we're talking about awareness, screening as an enterprise. If it just happens and no one tells it, they get very little information ahead of time. But then afterwards they never get a report saying we checked these 50 things out and everything is okay.

That would be another touch point for public awareness. And so I don't know if that's known or if you view that as -- I mean, obviously there could be some complications around it, but our

committee, I think, would be glad to talk with you more about that.

DR. BOYLE: I think both comments are terrific. The idea of the consequence of the diagnosis to the family is obviously an extremely critical issue. So it's maybe something that we can work together on, thinking through.

I guess I would defer to my clinical colleagues in terms of whether or not physicians inform families. My guess is no, but I will defer. Not something we've talked about in the subcommittee.

DR. KUS: Right, but I can give a specific part because a lot of times it doesn't happen. It's kind of the idea that no news means good news in docs. But there is -- I'm working with a group that has a HRSA grant called Bronx ongoing pediatric screening in the medical home. And one of the outcomes of it is the issue of newborn screening. And so we're monitoring and developing a process where first you check that newborn screening results get in the chart, and then there's a discussion with

the family, and they're monitoring the practice. And hopefully this will be exportable statewide and nationally. It's really been -- made a huge difference. It went from kind of nothing to having this discussion, and I think it fits particularly with your education part, because I don't think it's a standard of care right now, and this really moves it.

DR. TARINI: And so the AAP's Quality Improvement Network, the last project that was just completed, addressed this issue of generally acknowledging that in practice it's probably the fact that most physicians are to go by this no news is good news, and demonstrated a successful intervention in the Quality Improvement Network they were able to get the primary care physicians to discuss and document normal results with the families.

Of course, as with any of these, dissemination widely is a challenge. It can be done. I think both of these projects recognize that it can be done, and it has positive consequences.

That's always the challenge is dissemination.

DR. GREEN: Thank you. Nancy Green, Columbia University. So, Coleen, I'd like to suggest to you or, I guess, your successor for this workgroup, another area to consider thinking about, the challenge of looking forward. And that is as we -- and this probably presages my presentation later this morning. But I think the category of disorders for which there's newborn screening, that the treatment is transplantation, either hematic stem cell or, in fact, organ or anything else.

I think that's a group of conditions for which, in fact, the outcomes are complex. And I would just suggest that the subgroup might want to think about those as a group and tracking what that means. Certainly for SCID, which is, you know, a somewhat special condition, that's being organized very well. I just came from the primary -- SCID, whatever the transplant group that's organizing around that.

So that would be a readily accessible resource that Rebecca Buckley, for example, or

Jennifer Puck has been very involved with. But for the other disorders, I think that -- it's a less focused area, and it could be helpful for the group to focus on. Thank you.

DR. HINTON: Cindy Hinton from the CDC, and I just wanted to follow up on the pediatrician education part of it.

So following up on the Quinn project, we have had a paper accepted for publication by pediatrics that talks about the Quinn experience, and pediatricians learning to inform patients. And also building on the Quinn experience, CDC funded AAP to develop an EQIP online course to talk about the experience with the patient, informing the patient. And that's almost ready for prime time. I think some time this year it will go live on the AAP website, and then pediatricians can take that for MOC part 4 credit. But a key part is informing your patients about newborn screening, closing that gap.

DR. HOMER: So I was going to mention the Bronx program and Quinn. So those have been covered.

I did want to at least bring to the committee's attention, the subcommittee's attention, a couple of relevant activities. So my organization has had the pleasure of working with HRSA Maternal and Child Health Bureau for many years on how to improve this issue of follow-up for newborn screening. And we have actually a great deal of experience on how to improve this process of complex negotiation and complex handoffs. There are a variety of tools, and particularly I'm excited about the current method we're using, which is the use of a variety of checklists at different places. Again, sort of building on a tool, a theory of checklist manifesto as a strategy to deal with some of the complexity of these hand-offs. And I think that's a very valuable strategy.

Another HRSA initiative related to this sickle cell conversation, which will come up later, is we have the good fortune to be in the National Coordinating Center both for the newborn screen program and with the sickle cell disease treatment program. And the concept there is to engage both of

those communities in a coordinated effort to examine their own performance modeled on something like the cystic fibrosis model of examining their patient population, examining variation.

The challenge there, and again the paper that we'll be discussing later is that at least for much of this population, especially on the adult side, caring for adults with sickle cell in centers does not seem to be the method that is working for this population. In other words, most adults are cared for in primary care settings. So I think we really need to look at different strategies for engaging primary care medical homes and how to coordinate that. But again this concept of using a variety of national information systems.

That leads to the issue which I was going to bring up in the Testing Committee, but I think it more appropriately belongs in this committee, is how are we interfacing with the electronic health information system revolution? I mean, even in the last three years we've seen primary care adoption of electronic health records go from 10 percent to 40

percent. It's only going to go up. And clearly that will be a very powerful vehicle for linking data from newborn screening, which is presumably part of meaningful use, but also, again, feedback loops on whether that information is being used.

So I think we probably need some subcommittee of one of these committees -- probably the Long-Term Follow-up Committee -- that specifically has an effort on the interface with electronic health information systems.

DR. BOYLE: Can I just respond? So thank you very much, and I look forward to -- you are a member of our subcommittee, so we look forward to your guidance on both issues, both hearing as well as sickle cell disease.

And in terms of the electronic health record interface, the committee did have a workgroup at one time on helping to better understand how we as a committee could help facilitate that work. So I guess I'm going to turn to Sara in terms of where that -- what the status is and whether that's an issue that we should all be considering as an

overarching, a cross-cutting issue, or really where that falls.

DR. COPELAND: Which workgroup in particular?

DR. BOYLE: It was a workgroup on HIT issues, youth case, health standards, just the complexities of making sure newborn screening, you know, quality measures, as well as -- are developed as well as the integration of it.

DR. COPELAND: It was retired. The workgroup itself was retired. And then the membership was kind of integrated into the various subcommittees.

DR. BOYLE: So as subcommittees, thinking of our own charge, should one in particular be thinking about that? Is that something that our subcommittee should be giving consideration to since it's no longer a separate workgroup? I guess I'm just looking for that.

DR. COPELAND: Well, HIT is such a broad area, I think that you need to be -- it would need to be very clearly described as to what role you saw

your subcommittee playing with HIT because the Lab Standards Subcommittee is working carefully with NLM in terms of terminology and making sure that we can provide NLM with some feedback for lock codes, et cetera.

But in terms of involvement with HIT, I think that clinical decision support, et cetera, in conjunction with -- or being aware of the other projects that are working on, and maybe being informed by them would probably be the best bet. But I don't know that I would take up the banner of HIT under one subcommittee.

CHAIRMAN BOCCHINI: Steve?

DR. MCDONOUGH: I think it would be part of education and follow-up for both. As physicians, we have this HIT, you know, come to our offices. We were going to document that they discussed the newborn blood spot, or that we gave them the results, made sure that they got the results of the hearing screening. That would be -- I guess would be all three because you can document it. But I see particularly with education and follow-up with HIT,

the committees ought to be following up on that, and monitoring what's going on, and how they could be implemented.

DR. ZUCKERMAN: Alan Zuckerman, Consultant with the National Library of Medicine, who was co-chair of that HIT workgroup. And I just want to second the notion that these issues are complex, but some of them are reviving and very relevant to different committees within the group.

At one time we had considered the need for standardized quality measures in the proposed stage two regulations. Some of these measures on follow-up of hearing screening or one of the options that people can use in the incentive program.

And I think the more interesting focus for the long-term follow-up group will be on incorporating genetic data and the data needed for follow-up in the EHR. And there are active requests for comment on getting issues, such as pedigrees, into EHR, the ability to share data, pass on newborn screening results as children move through childhood, and other similar issues where the EHR

should become a source of data for follow-up.

But perhaps the greatest challenge will be electronic formats recording plans of care to share between specialists, primary care, and families. This has been a subject of discussion in the subcommittee. Hopefully more attention will go to that so that children identified through newborn screening will have documented care plans available at multiple points of care.

CHAIRMAN BOCCHINI: Thank you, Allen. Carol?

DR. GREENE: Thank you very much. And I'd also like to go all the way back to the priorities, the charge for the committee. And the same thing is to ask, is it time to -- does the committee want to ask the subcommittee to stay confined only to newborn screening conditions, or is it time to look at, you know, lab education? Is it time to look at the long-term care of children with genetic conditions, even if they're not newborn screen. And as we were discussing the priorities for the future,

we were reminded that our charge is newborn screen, and that we couldn't go beyond it, so we would need guidance from the committee in order to look beyond the newborn screening disorders.

CHAIRMAN BOCCHINI: I think the charge of the committee includes screening and evaluation of public health impact for -- input to heritable disorders independent of newborn screening. I think, as indicated, as we've kind of reviewed what the committee has done, newborn screening was sort of the focus in the beginning because it had the greatest opportunity for impact. And so there's no -- we don't need to stick with that alone. I think we do have the opportunity to look at other aspects of heritable disorders.

DR. GREENE: Obviously from my comments, I love what you just said. Thank you. And I think we need to have some specific guidance from the committee to operationalize that because I completely agree with what you said that the charge of the committee is broad. The charge of the subcommittee, which Coleen very wisely started, that

that's what's guided our priority development. And the charge of the subcommittee has in each of the three elements of the charge, really it's newborn screening.

CHAIRMAN BOCCHINI: We need to make sure that that's part of the evaluation. I agree. Don?

DR. BAILEY: So this is more of an overarching comment across the three subcommittees and the maybe the committee itself.

So I remember one or two meetings ago, Jeff Botkin raised the question of should we have another subcommittee on ethics. And in your question earlier, you kind of prompted this again.

So I think there are a couple of things. One is that we could each make sure that our three subcommittees are thinking about ethical issues, whether it's in follow-up or, I don't know what would be -- I can't imagine what the lab ethical issues are, but I'm sure there are some. And certainly some are related to education and training.

Should that be a -- and this is an example

of how can we integrate things across our subcommittees when there's a common theme around something like ethical issues. How can we have a shared conversation about that, or whether there should be another group that actually focuses on that.

I'm sure there are other issues like, you know, moving from parents coming with a problem on their child to a diagnosis that probably fits under this committee's work, but is not kind of directly aligned with one of the subcommittees right now. So I think it raises a broader question about how do we deal with things that are not necessarily the single assignment of one subcommittee, but probably are important activities for our committee as a whole.

I don't have a suggestion right now, but I think we should raise it.

CHAIRMAN BOCCHINI: Yeah. I think it's an important comment, and I think the most important part is that those things that are overarching, that there's good integration amongst the leadership of the subcommittee so that those can be addressed

across the subcommittees. And certain issues, like ethical issues, I think fit under the purview of each of those committees, and may not need a separate subcommittee. So I think that's a good consideration for us to have. So we need to make sure that that's being addressed as we look at the subcommittee rolls.

Chris?

DR. KUS: One comment that I think relates to the whole committee, and also follow-up and treatment is as we're going through this process, there's the whole discussion about essential health benefits relative to the Affordable Care Act, which is a State decision point. And my concern is that there will be children in some States where they may not have coverage for conditions identified for newborn screening. And that just doesn't seem like a good way to go.

So however we talk about this, I think we want to make sure that children have access to care and insurance coverage for that care.

CHAIRMAN BOCCHINI: Thank you. Other

questions, comments? All right. Thank you each for your presentations, and this is a very good discussion. And a lot of important comments that I think will inform the subcommittees as they meet this afternoon and further hone these priorities and specific projects. So thank you all.

Next on the agenda is update on RUSP conditions, and we're pretty much right on target. And Cynthia Hinton from the Centers for Disease Control, National Center on Birth Defects and Development Disabilities, is going to present an update for us.

DR. HINTON: Thank you. I just want to give an update on work that a collaborative group has been doing developing surveillance case definitions for newborn screening conditions.

So the context for these surveillance case definitions is that we have a lot of genetic testing and newborn screening going on, and the numbers increase all the time as the types of conditions that we are going to be collecting.

And we've moved towards uniformity in the

newborn screening panels and performance metrics. But if you're looking for practice to practice, state to state, what counts as a condition in one State or one practice may not necessarily be what another physician or State would classify as that particular case.

So as we move towards having standardized panel collaborating among States, regions, centers, to combine data, we really need to have some standard case definitions that as cases are looked at or, you know, as conditions are looked at, one person can look at any particular case in that data system and know this was the definition that was used to include it.

So this will allow for harmonization across data systems, programs, patients, and actually now I qualify that because this really doesn't have anything to do with patient care and how you as a physician will treat your patients. This has to do with how we as a public health system or clinical center is interested in research would classify cases.

And the legal imperative to do this goes back to the Newborn Screening Saves Lives Act in 2008 where the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children shall consider ways to ensure that all States attain the capacity to screen for the conditions. And part of that is the coordination of surveillance activities, including standardized data collection and reporting, harmonization of laboratory definitions, confirmatory testing and verification of positive results, in order to assess and enhance monitoring of newborn diseases.

I also want to talk about why a surveillance definition and what is a surveillance definition. And this comes from the CDC's MMWR back in 1990. I have the reference there. But it's an article about case definitions for public health surveillance.

So it is of foremost importance to precisely define what will be considered a case in order to accurately monitor trends of reported diseases, detect their unusual occurrences, and,

consequently, evaluate the effectiveness of intervention.

Now you can see, this really comes out of an infectious disease model. That's really where surveillance first took its stand in public health is counting infectious diseases. And I'm sure many of you are familiar with the CSTE's reportable conditions and case definitions that have developed for that. It's moved on for cancer, birth defects, developmental disorders. But, you know, having a uniform way of identifying cases to keep an accurate record of what's going on in the country and the State and the region.

So the usefulness of public health surveillance data depends on its uniformity, its simplicity, and its timeliness. So as we combine data from States' and regions' programs, it's really essential that we have some standard definitions to work with.

How does a surveillance definition differ from a clinical case definition? So the surveillance case definitions are intended to

establish uniform criteria for disease reporting, and that's disease reporting back to your newborn screening program in the State to a regional collaborative. Or if you are working in a clinical consortium, to report back to that clinical consortium.

They should not be used as the sole criteria for establishing clinical diagnosis or determining the standard of care necessary for a particular patient, presenting guidelines for quality assurance, or providing standards for reimbursement, or initiating public health actions. The use of additional clinical epidemiologic and laboratory data may enable a physician to diagnose a disease, even though the surveillance case definition may not be met. And, again, this comes from CDC definitions for case surveillance definitions.

So when I think about this, I mean, one of the things I think about in terms of, let's say, pertussis, because I have some experience in investigating an outbreak of pertussis. Public

health officials do not wait to actually culture the bacteria or run PCR. They see something happening. They go out and they start investigating and treating. And that would be initiating public health actions.

Kids are getting treated. Families are getting treated appropriately. And yet as a public health agency, when you go back and you actually want to keep a record of how many cases of pertussis that we have, the CSTE, the Council of State and Territorial Epidemiologists, has a very standard definition. This is case, a definite case. This would be a probable case. If you could grow the bacteria, it's definitely a case. You couldn't grow it, but you did some PCR, it's a case. You know, cough greater than 14 days. And that's the type of thing that as we went into this process, we really wanted to have for the newborn screening conditions as well.

So the goals of this initiative were to develop a model for the categorical determination of diagnosis of newborn screening disorders for public

health surveillance. We wanted to refine a model that would be comprehensive and useful for these conditions, and build consensus on case definitions from stakeholder groups. That's pretty much where we are right at the moment.

After that, we would like to present the case definitions to this committee for approval, and, if approved, move forward to the Secretary for approval.

So we convened gatherings of subject matter experts in hematology, metabolic genetics, pulmonology, immunology, and endocrinology, and through conference calls, face-to-face meetings, and web-based interactions, we started to discuss potential case definition models. And there were three models that we worked with that I will go into. They were a quantitative, a tier, and a diagnostic model.

The quantitative model -- and this is an example of it for, I guess, a metabolic condition. But it would be looking at various types of aspects of diagnosis or presentation with newborn screening

results and assigning a number to each of those diagnostic categories. And if you had a certain level, it would be considered definite, probable, or possible, or unlikely.

The tier model would be, you know, starting off with a newborn screening result, and then kind of going down through this diagnostic algorithm to establish whether something was definitely a case or probably a case.

And then the diagnostic model would be looking at a condition and then setting just some very basic diagnostic categories. Did it meet -- you know, how many mutations, or, did you do a mutation and do this type of assay, definitely a case. Possible, you don't have what would be in the definite, but there's definitely a profile that someone would consider a case.

So we did some pre-meeting work looking at these different models for each of the expert groups, you know, what are strengths and weaknesses, can you identify gaps, can you apply this to your own cases. Just to, you know, hit the ground

running.

We met face-to-face last June. And last June we had the immunology group, the cystic fibrosis, hemoglobinopathies, and metabolic group come together to start working on case definitions. The endocrinology group met by conference this past fall, and the metabolic group just finished up this past February. And each group pretty much decided which of these diagnostic models they felt met their criteria.

So for the case -- this is just an example. The case definitions for the hemoglobinopathies, they looked like they did the tier. They did more of that tiered algorithm model. SCID did that scoring model where they decided what would be, you know, SCID possible DiGeorge, others. And so they worked through the, you know, clinical presentation, assigned points, lymphopenia, the lymph function, molecular, and assigning points. And then if you added those up, you would have a definite diagnosis possible.

CF is really more of that diagnostic

criteria. You know, it's a definite case if it meets this and this. And then the endocrinology also used that diagnostic criteria of what would meet primary congenital hypothyroidism, secondary, which we did secondary congenital hypothyroidism, TBG. They also did this for the congenital adrenal hyperplasia.

And, I mean, the metabolics, we had to work through, you know, 27, 28 cases to come up, but also worked on that diagnostic criteria, mainly looking, you know, if there were mutations that had been done, or if it was mutation plus enzyme, or if you just had the metabolic -- I mean, the biochemical. And then if we were able to state what would not be a case, we included that, or what we felt was an incomplete case.

So these were -- these are still considered, you know, in a draft format. These have gone back out to the regional collaboratives for the regional collaboratives to share with subject matter experts in their group. And primarily they're looking at that diagnostic criteria. You know,

would you as a clinician consider this as a case?

And I guess what we're still running into is there are a lot of things that clinicians would consider a case and treat. But if you were to look at this broader surveillance case definition, you may not look at it as a case.

So when we get this feedback to us, we are going to look at it again and see what the experts in the regional collaboratives have said about these various diagnostic criteria. But really the point of these criteria are going to be very simple, very broad. These may be people who would go back and define a case, and they're not necessarily the clinician or the nurse. I mean, it may be someone more with a clerical background or someone who's been trained as an abstracter.

So the idea would really be to get these as simple as possible and to realize these are not dictating how you treat a patient or what patients that you treat. But we really are interested in getting the feedback in case we've missed something, you know, a criteria that's very important in coming

up with these case definitions.

Then through APHL, we're going to be working directly with the State newborn screening programs. That will then go back and look at their cases for a year and see how many of the cases that they have meet these public health case definitions. So it's to really put them in action and see, you know, can you define cases? Have we actually inadvertently left some areas of overlap where you cannot get that clear cut definition.

So to continue to monitor these, you know, over time and see, you know, do they work, how can we revise these. And the idea would then be to have these approved and to use them as national surveillance for newborn screening disorders.

There's already been interest from Australia, New Zealand, you know, people that have national definitions for public health newborn screening surveillance. So I think that, you know, these definitions are going to be very important both nationally and internationally as we move forward with them, and with CSLI, and, you know,

other public health organizations.

There's been a lot of people that put a lot of work into them -- Sara and Debbie organizing through HRSA. Federal and other partners have been part of the facilitators for these expert groups. These are the people that participated in these initial expert panels developing the initial draft of the case definitions.

And so that's my contact information, and that is where we are with this process.

CHAIRMAN BOCCHINI: Thank you, Cindy. That's a great summary of where you are and the amount of work that's been done to get to this point. So thank you.

This is open for questions now. First, Don, then Steve.

DR. BAILEY: So a couple of things. Do you envision a national tracking system then ultimately where all of these conditions, we would be able to say every year with confidence that we have this many actual clinical cases of these conditions?

DR. HINTON: Well, in a way we already have that through the Newborn Screening Genetic Resource Center and the NNIS. And it's voluntary for States to contribute to that. And the definitions that are used for that are still very much at this, this is what the State used as a definition, or, this is the State and more has to do with what was a collaboratory cutoff for that.

So there is an opportunity to have a type of national tracking or a national data collection. And so I think that at some point these definitions could be used in a system like that.

The NBSTRN is actively working on a clinical -- the virtual data dried blood spot repository. This could play into that, although I think that for that type of research, they're going to be getting much more granular the types of things.

So I actually do see how these would be useful either in refining data systems that are going on, but definitely at that State and even a regional level. And then being able to compile

those, whether through CDC or through HRSA, and have a national report. But, you know, we've got the bones for it right now.

DR. BAILEY: And, secondly, do you see this as an ongoing activity or a one-time activity?

DR. HINTON: This is an ongoing activity, and we haven't really talked at the, you know, the level at which this would be revisited. But for any of the standard reporting, I'm thinking specifically about the notifiable conditions. CSTE meets on a regular basis, and they will refine their case definitions. And their case definitions are refined on the basis of the type of research that will be coming out of the NSBTRN or about new clinical practices. You know, how do you refine the diagnosis? What do we start to learn? And that information will be fed back to a group.

And I'm not sure exactly, you know, what group it's going to be. But these will not be static. They will be revisited as we learn more about diseases, and we can refine the case definition.

DR. MCDONOUGH: I want to compliment you on your wonderful work. It's outstanding. Are you planning on having this coming back for our September meeting to act on? Do you think the timing will be for that?

DR. HINTON: I turn and look at Sara. I honestly don't think that we will be that ready.

DR. MCDONOUGH: Ready?

DR. HINTON: I know that the regions have asked for a little extra time in reviewing the case definitions, and I think Debbie and Sara, maybe January we'd be back. But by the end of May, the regions are supposed to review it. And so I think -- yeah, Sara says January may be our best bet of coming back and reporting.

DR. MCDONOUGH: Is there any coordination between CDC and the State health departments on releasing annual data telling the public, policymakers, the media, about the great work that you're doing, and the benefit to society, what's being done? Is it how good are the State health departments in doing that? How good is the EC at

doing that? Is there any coordination on metabolic screening month, when that has occurred?

DR. HINTON: No. That's definitely -- I mean, if you look at the CDC definition of surveillance, it's not just the collecting data in. It's the getting data back out. And I think, you know, probably what we would have to do is just make a more active push in getting data, like CDC releases annual reports on cancer or other things. We do it for birth defects with an annual report.

And I think perhaps getting that back out, it sort of fits in with the type of awareness is that you collect it and get it out. But that may not be directly what you're getting.

DR. MCDONOUGH: Well, I think it's a very inexpensive way to get the message out about what it's doing. Basically you have a news release. You put a stamp on it, and you send it to the media, and you have interviews. And maybe it's not the best way to coordinate on a monthly basis to have the States do it, but I think it's very important to encourage State health departments or public health

labs that are not part of, or labs that are not part of State health departments. Because the media is always very interested in facts and information. That's a great, inexpensive opportunity to promote what we're doing.

DR. HINTON: Well, through CDC, we do that through the MMWR, the mortality, morbidity weekly report, and that oftentimes comes with press releases, and it is a very standard, you know, way to get information out and get it out quickly. And I think if we were to highlight new surveillance case definitions and then, you know, do a report, that could be a way that, you know, we come out with annual or biannual reports on newborn screening.

I don't think that State health departments are going to be able to do it on, let's say, a monthly basis. Newborn screening conditions can take a long time to actually come up with, you know, an accurate --

DR. MCDONOUGH: I didn't mean to suggest a monthly basis. I was saying maybe once a year during a particular month there would be a big push

for everyone.

DR. HINTON: September is Newborn Screening Awareness Month. We do it for birth defects and MMWR.

DR. BOYLE: I think that's a great idea. If we could actually have a surveillance summary that came out, whether it's the MMWR. The only MMWR is nice is it does public health and State health programs activities. If there was a year that, you know, a month that you had your report filed every month. I mean, every year. And you could bring attention to that. I think that's an excellent idea. I just don't know that from a State health department feasibility perspective you could have data for, you know, 2011 reported in September of 2012. No.

DR. HINTON: Right. We may not be able to have an update like that. I mean, surveillance case definitions, surveillance data sometimes can be two or three years behind the actual case. And that has to do a lot with how long it can take to clinically identify a child.

DR. BOYLE: But just to take the issue a little further, I mean, could you have a presumptive case, you know, that presumptive case gets clarified, you know, over a year period of time, and then your next report clarifies that? Anyway, just a thought.

DR. HINTON: Well, I think when we approached the -- I know for the metabolic and possibly others, we do have that, you know, definite, possible, you know, or probable, possible. It is capable or it just, you know, could be sort of a, you know, metabolic disorder in general, like pertussis is cough illness. I mean, we could have something like that. And I think it varies from category to category how the groups felt they wanted to portray that.

DR. COPELAND: And we're also, as we go to validate this in the State, newborn screening programs, we will have an in process category because we realize that, A, this is retrospective, and, B, some things take a really long time to get resolved. And so there will be an in-process

category that can be updated as time goes on.

CHAIRMAN BOCCHINI: But even if you present data that's from the prior year, as long as it's understood that that does take a period of time to determine -- make a final determination, I don't see that as a real problem as long as it's explained as to why the data takes that long to come out. I mean, yeah.

DR. HINTON: I don't see it as a problem. I think as long as we have, you know, the very clear definitions of what we used and that explanation, you know, the time it takes to define cases, I think that works.

CHAIRMAN BOCCHINI: I agree. Dieter?

DR. MATERN: Yeah. One comment to Sara quickly. In Minnesota, we know now that it takes 71 days to clear up a case based on the Supreme Court decision.

(Laughter.)

DR. MATERN: But otherwise, I'm intrigued that the groups for CF and the others differentiate between disease severity whereas the metabolic group

just calls it, for example, the LCAD, but doesn't say early onset, late onset. Is that something that's going to be considered in the future?

DR. HINTON: I don't know quite frankly, but I think what -- and Sara may remember about the discussions. But I think, you know, this late onset, early onset, or the severity, I think we went through thinking about, you know, like whether to put specific levels in versus not specific levels. And it just started getting too complicated. And we really wanted to take it down to a very simple level.

DR. COPELAND: Well, I think with the RUSP panel, I don't know that we could -- I don't know that we necessarily know, at least for the LCAD, what's early versus late. But, say, if Pompe were to get added, I think that there's better clarification genotype, phenotype. And as we learn more, we probably will be able to differentiate that because the idea is to detect those with early onset.

DR. MATERN: In that case, I would just

always make sure that you have a disclaimer because, I mean, you state initially that everything should be very well defined, so you have to make sure people understand that there are still variability.

DR. GREENE: So I am one of those people who haven't yet actually looked at for comment, and I got to say it's a great presentation, and I appreciate the process and the opportunity to comment.

From what I saw in the slides, I'm sure you've heard a lot about concern in the inborn errors of metabolism, that it looks like there might be a lot of emphasis on the DNA, but it is still the biochemical phenotype against which the DNA is measured. But I appreciate that I will have an opportunity to comment on that specifically.

So what I wanted to say at the level of the committee is, I think we have a major educational need here, and that is the presentation, and I appreciate it. But it then have to argue it with the State health department and with insurance companies, going back to the original article and

the point that you hammered home that a case definition for surveillance does not mean that you don't treat the child.

DR. HINTON: Right.

DR. GREENE: And we've had experiences where something doesn't meet the case definition, and so the newborn screening laboratory following the case definition tells the primary care physician that the case is closed because the child doesn't have the classic disease. And then we upset everybody by going back to get them. And one child who actually fell of the face of the earth and didn't come back until she was symptomatic and MSUD coma because somebody said she didn't have classic disease, but needed to come back, but that was translated as into didn't have disease.

So I think we really need to maybe ask -- and maybe it would be in the Education Committee. But I think this has to come with a lot of education for public health, for providers, for insurers, to really hammer to the larger group what you made so clear here. These are surveillance definitions that

if you don't meet the case definition for surveillance, you still -- you know, like the pertussis example. You still could die if you don't get treated.

DR. HINTON: Right.

DR. GREENE: And I think we need to focus on that educational need.

DR. HINTON: And for birth defects, I mean, in some States they may be reportable or not. That's still a child that is going to need special services. But if you're collecting data for the congenital defects registry or it's going into the birth defects prevention network count, they're using a standard definition, so they all know what each other is talking about when they report the case.

And part of it may also be the timing. You're dealing very real time with a child who has been identified through newborn screening that you're getting in for a diagnostic workup and immediate management, whereas, let's say, a year later or two years later, someone is going back then

through, you know, for their standard report that goes to CDC or whoever. And is going back and then refining, well, you know, let's apply our case definition. What did we have? They're not exactly related, you know, in a time dimension there.

DR. GREENE: Right, and not only not related in time, but not related in different ways people use the data. So the State of Maryland then may find that they've got, you know, six kids with this disease, and you add it all up, and Hopkins and Children's National, and University of Maryland says we're following 1,000 kids with inborn errors of metabolism, and we need this level of support from the State. And somebody says, no, no, no, no, no, see, look at the surveillance data. You've only got 400.

So we need to be sure people are educated to know what those data mean and what they don't mean, and that they don't misapply them either on an individual basis or on a programmatic basis.

DR. HINTON: Well, and also then to have the definition set so, I mean, that you're not

having such discrepancies, you know, that you're capturing -- as anything, you're capturing enough, but you feel certain about what's there.

CHAIRMAN BOCCHINI: Questions or comments? If none, Cindy, thank you again very much. I look forward to subsequent presentations. Thank you.

All right. I think we're ready for about a 15-minute break, so we're going to return here at 10:45.

(Break.)

CHAIRMAN BOCCHINI: Okay. I think we have a quorum to get started. Could I have everyone's attention? We're going to reconvene the meeting.

Next on the agenda, the committee has received two nominations of conditions for consideration to move forward, and the Nomination and Prioritization Committee has met and reviewed both of the submissions. So we're going to first start a discussion on MPS I with some public comments. And then there'll be a presentation of summary of the nomination, and then a discussion by the committee with a vote as to whether to proceed

to move this nominated condition to the Evidence Review Group.

So the public comment period is 15 minutes. We've asked that each of the individuals who are going to make public comment limit those comments to three minutes so that everyone gets a chance to make their presentation. And we're going to begin with Diane Kane, who represents the Run for ALD, Incorporated. Is Diane here?

DR. COPELAND: And I want to warn everybody ahead of time, I am going to be rude and interrupt. You may even hear the timer go off because otherwise we'll run out of town. Otherwise I don't like to be rude.

MS. KANE: Mr. Chairman and members of the committee, my name is Diane Kane. I'm the president of an organization called Run for ALD, which was founded by my late husband, Jack, after he was diagnosed with Adrenoleukodystrophy 10 years ago. ALD is a neurodegenerative disease accompanied by adrenal insufficiency, and is often fatal in males if they are not diagnosed and treated in time.

I'm here today on behalf of a number of ALD advocacy organizations, including the Stop ALD Foundation, the Mile End Project, the ALD Foundation, ALD Life, Stop ALD, the Australian Leukodystrophy Support Group, and the European Leukodystrophy Association, to support the addition of Pompe and MPS I to the recommended Uniform Screening Panel.

Like ALD, these disorders are ones which can be successfully treated if identified early. It is our understanding that the Mayo Clinic is testing a new method that combines the newborn screening for lysosomal disorders, including Pompe and MPS I with screening for peroxisomal disorders, such as ALD. Therefore, it seems possible to screen newborns for all three disorders with the same testing infrastructure.

We will be submitting our nomination for newborn ALD screening for your consideration at the September 2012 meeting. It is essential that we identify babies born with ALD so that they can be given therapy for adrenal insufficiency. Babies who

test positive also need to be followed closely with serial imaging and other testing so that they can be offered hematopoietic stem cell transplant at the beginning stages of neurological disease. Early intervention dramatically alters the outcome of ALD and saves many lives.

Thank you for your consideration and for allowing me this opportunity to express our support for the nomination of the newborn screening test for Pompe and MPS I.

CHAIRMAN BOCCHINI: Thank you, Ms. Kane. We appreciate that.

Next is Bill Morris, Gray's Gift Memorial Foundation.

MR. MORRIS: Chairman and honorable committee members, my name is Bill Morris, as he said. And I'm here with the Genetic Alliance Consumer Taskforce. And this is a group comment representing 10 individuals on this taskforce.

This comment is our personal input and not an official position of the Genetic Alliance.

We are concerned about closing the gaps

for consumer taskforce awareness. Today as we come together as Baby's First Test Consumer Taskforce, to ask the Secretary's advisory committee for assistance.

We are all here today as concerned and invested consumers of the newborn screening process. Through our advocacy efforts, we hope to close some of those gaps that we feel as parents must be addressed in order to adequately help and every child affected by heritable disorders to have a long, healthy, and productive life.

We would like to commend and applaud the committee for the huge strides that have been made in adding screening to the recommended panel, and bringing uniformity and awareness to the ever-expanding field of detectable and treatable heritable disorders in children.

The gaps that we would like to focus efforts as advocates are: what screening is available and recommended, and what is actually tested for in each State. Each State is different. Awareness at the primary care level with the

pediatric so that warning symptoms may be caught, preliminary testing can begin, and referrals can be made as early as possible for the disorders that are not currently being screened for and/or have a later onset for the disorders.

Communication and education with both the healthcare providers and the public about newborn screening, being told that your child has a positive newborn screening and that the treatment protocol options and testing should be. Standards for care and best practices that make the newborn screening system practical and effective for those with heritable disorders.

Our hope is to close the gap between that screening is available and recommended by this committee and what is actually tested for in each State.

This one tops the list. We are asking the committee to further encourage the States to implement screening for all the recommended uniform screening panel and the secondary conditions by 2015.

I was a taskforce member and a father of two -- not one, but two sons that have genetic disorders. My oldest has PKU and was identified through newborn screening. My youngest died from Krabbe's disease in 2008. For me, the lack of general understanding between -- in the public of newborn screening awareness is tragic and dangerous at its worst.

For instance, everyone knows that children receive immunizations. All parents know about that. They are aware of it. But the number of parents that are aware of newborn screening and the role that it plays in the ever-expanding number of rare disorders, many that can be controlled with interventions and case specific treatment, have a very specific window of time to be able to allow for that treatment.

We parents are working at our State levels to get those panels implemented, but we need the assistance from this committee to have a greater impact on awareness in actually getting every child in every State screened for all 57 disorders. We

are already -- there are already so many factors that affect health of a child. Which State you live in should not be one of them. Thank you very much.

CHAIRMAN BOCCHINI: Thank you.

Next we have Christy Wees from Baby's First Test.

MS. WEES: Thank you. I'll be addressing gap number two.

Through awareness we hope to close the gap between metabolic, genetic newborn screening awareness at the primary care and pediatric level so that warning symptoms may be caught, preliminary testing may begin, and referrals can be made as early as possible, especially for those disorders that are not currently being screened or, or for the later onset of those disorders that are.

It is our hope that this committee will provide further training and information to pediatricians through the American Academy of Pediatrics and PCPs so that these disorders are not misdiagnosed as autism, bipolar disorders, speech delay, failure to thrive, developmental delay,

mental retardation, cerebral palsy, epilepsy, reflux, or colic, by practitioners who may not even know to screen for metabolic disorders beyond that newborn screening period.

As a taskforce member and mother, this experience -- I've experienced this gap firsthand as my three-year-old daughter is suspected of having a mitochondrial disorder with symptoms starting at two weeks of age.

After nearly three years of testing, seeing 14 doctors and specialists, we still did not have a confirmation or a treatment plan. Metabolic testing was not even considered by medical professions in nearly a year and half of escalating symptoms.

Gap number three: as a study was published in the *American Journal of Obstetrics and Gynecology* in May 2005, it showed that there were also gaps in communication and education with both the healthcare providers and the public about newborn screening. Therefore, we believe that closing the educational gap amongst healthcare

providers, making education for parents more consistent when there is a result, positive or negative, and exploring how to ensure more accountability at the State health department level, that each family is being educated about newborn screening. Resources available during that prenatal period is essential to us.

Consumer taskforce member, Chantelle Murray, remembers when her son was diagnosed with cystic fibrosis based off of an inconclusive newborn screen test. Although she went to a high risk obstetrician for prenatal care and was a neonatal nurse herself, she never received any education or information on newborn screening. And she found that she and her husband had a lot of questions about the results, not knowing who to turn to for answers and help.

Thank you.

CHAIRMAN BOCCHINI: Thank you. Next we have Ruth Caruthers from the Consumer Task Force.

MS. CARUTHERS: To echo Ms. Murray's concerns, Consumer Task Force member Amanda Beard

feel that the biggest gap with the current newborn screening system is that the follow-up care on the screening test is disorganized, inconsistent, and, in some cases, nonexistent. The lack of education provided to the people that work with the parents and to the parents themselves is very detrimental to the child's outcome. We acknowledge that they are professionals that have the desired education, but unfortunately those people are in a minority.

The lack of strict standard protocol awareness can significantly delay diagnosis and close windows of opportunity to get vital information about the child's disorder as well.

Mrs. Beard experienced this firsthand with her son, Wyatt, when he failed his newborn screening hearing test. His case was treated as if his abnormal test result was actually normal because the screening gives so many false positives. This went on for months, not knowing if he was or wasn't hearing impaired, and just sat in limbo. Now Wyatt is facing delays in speech and communication that can lead to behavior issues and learning delays.

Amanda has found through connections with early hearing detection and intervention that the results of the newborn screening hearing test are routinely not valued to be reliable or urgent by the professionals and parents, and are desperately seeking information and support in the time period.

It is her hope that the committee will acknowledge this need and fill in the informational gap with regulated mandatory education for all providers of newborn screening. This will allow them to perform the screening and give recommendations for follow-up more effectively, along with providing more consistent support to the parents.

It is amazing how far we've come in expanding newborn screening across the country, and this committee deserves a lot of credit for setting our national recommendations.

Task Force member Mark Ingman believes it is important for the committee to explore standards and best practices that make a newborn screening system practical and effective. Mark's son was born

with congenital adrenal hyperplasia here in the District of Columbia before D.C. screened for that disorder. He survived long enough to be diagnosed and put on medication, and is now a thriving teenager. If he has a serious illness or accident, he requires an emergency injection of hydrocortisone, and he would likely go into shock and die. However, if Mark wasn't there and an ambulance came to take him to the hospital, the paramedics would not have the knowledge, authorization, or medication to give him the shot that could save his life.

As private citizens, parents, and members of this task force, we will work with our local decision makers to make changes and spread awareness in the coming year. We hope that this committee would also look more closely at other elements of the newborn screening system beyond the screens themselves, and assist us in closing the gaps for future generations to come so we can all continue to connect the dots one blood spot at a time.

Thank you.

CHAIRMAN BOCCHINI: Thank you. Next we have Mr. Steven Holland, National MPS Society.

MR. HOLLAND: Thank you, Chairman and committee. My family is going to join me. I'll go ahead and get started while they get up here.

My name is Steve Holland, and we're from Fort Worth, Texas. I am president of the National MPS Society and am here today representing 800 families touched by MPS-related diseases.

I'm also the father of three MPS I children, and I'm here today with my wife, Amy, and my daughters Madison, age 20, and Laynie, age 18. My son, Spencer, passed away four years ago at the age of 18.

While several MPS I parents wanted to come speak with you today on this very important, we were asked to consolidate our comments into one. So I reached out to the other parents and incorporated their comments into mine.

I know that you've been presented with the science and the facts and figures about the disease, so I don't feel compelled to repeat those to you. I

just feel the need to present the parents' perspective on newborn screening for MPS I.

Once your child receives a diagnosis like MPS I, a parent feels an overwhelming desire to make things right by that child, to create as equal a playing field in life as possible for that child who obviously was born with a huge disadvantage of having a terminal genetic syndrome through no fault of their own.

One of the most important ways of doing that is by providing them with a medical treatment that will help prevent further damage by the condition and help sustain their lives, whether that be stem cell transplant or weekly replacement therapy.

The problem is that we cannot begin treatment until we know they have a disease. It often takes many months and sometimes years between knowing that there is a problem and getting a diagnosis. During this time, irreparable harm is being done to our children that future treatment will not be able to reverse. This delay in

diagnosis and treatment often creates parental guilt and regret for not following up sooner on these problems or for not forcing their pediatricians to follow up on these early symptoms when the pediatrician dismisses the parental concerns as complaints of an overzealous parent.

Once it is too late, parents realize that they lost that precious time when the early treatments could've forever changed their children's long-term clinical outcomes.

However, with newborn screening, all of this regret, guilt, and conflict with the medical community over delayed diagnosis is eliminated. Treatment by stem cell transplant and some replacement therapy or whatever new treatments around the corner can start immediately.

The evidence shows that the long-term clinical effects of MPS I can virtually be eliminated by early treatment, giving that child the level playing field that we as parents so desperately desire.

Now I understand that there are concerns

over false positives and the resulting parental anxiety that can create. However, such anxiety is short lived as compared to the permanent damage caused by the untreated diseases in the months or years following birth.

I predict that the recipients of false positives barely remember the event a few years following birth. I know that parents dealing with a delayed diagnosis and treatment remember it and live with it for a lifetime. What would my child be like if they only received treatment since birth?

Another important benefit from newborn screening would be reducing the births of affected siblings. In my family, all three of our children were affected, even though the odds were 1 out of 4 with each birth. Because our kids were born so close together and had an attenuated form of the disease, we didn't realize there was a problem while we were having a problem.

If newborn screening had indicated my son had MPS I, we would've used the benefits of genetic counseling to prevent my other children from being

affected. We know many families with more than one affected child who indicate that they would've done the same thing, reducing the overall prevalence of the disease and the resulting demands on society in general and our family specifically.

So in a nutshell, it just comes down to time and options. We have the ability to prevent most of the permanent damage caused by MPS I by providing parents with treatment options at birth. Let's do it.

My family, along with the other MPS I families, thank you for the opportunity to speak on this very important subject.

(Applause.)

CHAIRMAN BOCCHINI: Thank you very much for those comments.

We're now going to go to the Nomination and Prioritization Committee report, and Nancy Green will provide that report. Fred Lorey, who was going to do that, is unable to attend this meeting.

DR. GREEN: Okay. Thank you to the leadership of the committee, and to those who spoke

at public comment, thank you. It's very helpful.

So I'm actually supposed to be Fred Lorey, but we don't look alike.

(Laughter.)

DR. GREEN: I hope that Fred can come to the -- can attend the next meeting. I also would like to thank the HRSA staff for scheduling both of my presentations to frame the lunch period. So thanks.

(Laughter.)

DR. GREEN: Just for me. Okay, thank you.

Okay. So I think what we'll do is -- the schedule is to have me present the MPS I report, and then lunch, and then to come back for Pompe.

This is the Nomination and Prioritization Workgroup, and you can see that we're well served. So thanks to all on the workgroup.

So I'll present, as I mentioned, the review by the Nomination and Prioritization Workgroup, and then there'll be some discussion, and I guess vote today on the nomination whether to move forward to evidence review with each disorder taken

at a time.

Okay. So I apologize. These slides are packed, and I assumed because I needed such an education on these disorders, that many in the committee and in the audience would as well. So I'm going to go through this. And I always hate slides like this, so forgive me.

So the nominator for MPS I was from the National MPS Society. And if I mispronounce the name, I'm sorry. Barbara Wedehase.

So MPS I is a medically serious condition, and I think we've just heard eloquently what that means. It's defective in glycosaminoglycan catabolism, and there's a decrease or absence of the enzyme responsible for the catabolism of this product. The severe form is really very debilitating with symptoms that arise within the first year of life, and it's a multi-system disorder, so it affects cardiac pulmonary, the central nervous system, and other organ systems.

It's fatal normally within -- excuse me, and I'm speaking about the severe form. It's

fateful within the first decade of life with considerable central nervous system impairment associated with the disorder. And that's commonly known as Hurler syndrome, and the other less aggressive forms have other acronyms associated with them. And in this most severe form, there's an absence of the enzyme.

So based on the literature produced by -- supplied by the nominator and as well as expertise -- I would thank Dr. Matern for this -- and other literature, that about half of the cases are this severe form with, as I said, symptoms early in life. The attenuated forms are slower, and later progress. And I think that split between severe and other more attenuated, but serious forms are sort of typical, as I understand, of the lysosomal disorders. So some of the milder forms have little or no central nervous system involvement, and, again, sort of later symptoms and slower progression.

The estimated incidence of MPS I in the U.S. is 1 in 100,000. That includes, as I

understand it, all of those within the spectrum of disorder. And the actual incidence in the U.S. is not known.

Okay. So just to follow the format that the workgroup has used for evaluating these conditions and the nomination form, which I would applaud the edits, so we look forward to using those -- that edited version of the nomination next time.

So there is, in fact, a case definition. Spectrum, as I mentioned, the attenuated forms I won't have to describe. And all of the forms that I mentioned have little or absent enzyme activity, but the actual enzyme activity tested depends on the tissue tested. So whether it's a muscle biopsy or lymphocytes, perfo-lymphocytes can give varying results of enzyme level.

So that really then, as I understand it, requires a molecular analysis to correlate with the protein function. So the screening would be enzyme level and then diagnosis of the -- confirmation of diagnosis, and then characterization of the type of disorder depends on the molecular characterization.

We understand, I think, and Carol, actually you mentioned this in terms of the biochemistry being really critical for making diagnosis, that some variants obviously would have been previously unrecognized and may have variable impact on enzyme function and, therefore, disease. And then I have read that there's a pseudo-deficiency variant that's rare, and I don’t know how rare that is. But that also needs to be taken into consideration because, as I understand it, and I look forward to correction from my expert colleagues, that that is not a disorder, but it may how it classifies. So when I'm finished, maybe we can get some clarification on that.

Okay. So, you know, what's been the experience for the population-based screening and diagnosis, and what's the algorithm? So I refer to a recently published paper by the Wang, et al. that's referenced here, the ACMG Workgroup on Diagnostic Confirmation of Lysosomal Disorders published last year, which has established algorithms for MPS I, Pompe, and actually a number

of other disorders in a very complete way.

So the screening is by enzyme activity, by tandem mass spectrometry where the enzyme level is low, low or absent. Again, the absent level is indicative of the severe form. But there's some degree of uncertainty about that, about classification. And this disorder, like many of the other disorders, can be multiplexed with other lysosomal disorders as I'll mention in a moment. And that's certainly, I would say, appealing for the screening laboratory.

So according to this algorithm in the reference that I just cited, there needs to be DNA sequencing of the alpha-iduronidase if the mutation is obviously known, and then DNA sequencing of the affected enzyme. Now this reference does mention that again because there may be some uncertainty regarding genotype/phenotype correlation that sometimes family sequencing of family members for this particular gene might be needed again for novel mutations. And I think that's something that the evidence review group needs to consider.

And then the other issue is —— are there technical challenges for States that arise from the sequencing. Certainly as we know from New York that handled the Krabbe molecular diagnosis very well. We've heard -- this committee has heard those reports in the past, so it's just a question raised by the workgroup.

So the analytic validity for screening of MPS I. So Washington State has done anonymous screening of 75,000 newborns by multiplex. So they looked at three enzymes at one time, again by tandem mass spectrometry. And there were five identified cases below the cutoff level. And as you can see here, one was an early diagnosis. One was attenuated. One was a heterocygote carrier, and two had no identifiable mutation, and the false positive rate was approximated as 1 of 114,000. I think that refers to the enzyme level, and certainly not to the DNA diagnosis with the data for those five samples.

And then a number of States are in the process of gearing up for screening, so that hasn't been done yet. As far as I understand in Missouri,

the assay development is underway. Yeah?

DR. BOYLE: Just a clarification.

DR. GREEN: Please.

DR. BOYLE: How do you define what the difference between early and attenuate is?

DR. GREEN: So, again, absent of enzymes. So what I understand, Coleen, is the absent of enzyme, severe, aggressive form, early symptoms, and then the attenuating is the -- low level of enzyme and later -- and less aggressive progression. Yeah, thanks.

So anyway, as I mentioned, Missouri is in the process of setting this up, so we don't have it. Let me just finish this slide, Carol. And then several States -- New Jersey and California -- are currently deliberating about their screening approach. Can I just finish or do you want to say something? You want to correct something? Oh. Let me just finish. Maybe that's --

DR. GREENE: It's specific to this slide.

DR. GREEN: Okay.

DR. GREENE: The no identifiable mutation,

did they also look at you're an MPS and X-rays. I mean, do we know that just because there's no identifiable mutation, that doesn't mean they don't have it.

DR. GREEN: Sure. So these were anonymous samples, so they didn't have a connection to the baby.

DR. GREENE: So this could be an affected baby with no mutations now.

DR. GREEN: Of course.

DR. GREENE: Okay.

DR. GREEN: They may be promoter, you know, whatever. I don't know, in fact, how much of the sequence beyond the actual axons are sequenced in this paradigm, and actually maybe we can talk about that. These are important issues.

DR. GREENE: So that's an outside limit of the false positive rate. The false positive rate could be a lot lower.

DR. GREEN: So, again, I think the false positive rate had to do with the --

DR. GREENE: The two with no mutations

still could be affected, and the one with one mutation --

DR. GREEN: Right, so that's the problem with doing these anonymized sample screening, that we don't have those data. And you're absolutely right, the true/false positive rate, based on this screening paradigm, may be different and important. Thank you for the clarification.

Okay. So what's the clinical utility of diagnosing MPS? And, again, I thank those who participated in the public comment period. Certainly there's hematopoietic stem cell transplant for the severe form, which is best done by less than two years of age. The transplant, if successful, arrests the disease impact on the CNS and actually other disease manifestations.

And there was one reference in 2008 understanding that transplantation -- allogeneic transplantation is an evolving field. But at least in the publication from 2008, there was improvement in lifespan for those who were transplanted.

As we all understand, those of us who work

with transplanted patients for other disorders, that there's a 10 to 15 percent up front mortality associated with transplant, additional morbidity that's significant for host disease and other complications to be considered.

There's also an FDA-approved enzyme replacement therapy for MPS I. This is really designed for the milder forms because it does not cross the blood brain barrier, so that would not help ameliorate the CNS symptoms of severe form. On the other hand, it has also been used or proposed for use for patients who have the severe form who are awaiting transplant, who then may benefit from temporarily being treated by enzyme replacement therapy. So there are various applications for that approach.

Okay. So then this is sort of the punch line. What are the issues that the nomination group has identified, and what's the recommendation with respect to whether this nomination ought to go forward towards evidence review?

So just to summarize, there is a case

definition. There's screening and diagnostic protocols established, and treatment protocols established. And then there's the appeal of multiplex testing.

So the Nomination and Prioritization Workgroup has recommended that this nomination go forward for evidence review, so that's the proposal for the committee on the table. But the nomination group had considerable reservations about the nomination, and I've listed here the uncertainties that the group has identified, most of which I mentioned in the presentation -- the phenotype/genotype correlation, what do with those who are identified with the milder form since the nomination is in the context of newborn screening. Again, understanding that the attenuated forms are serious conditions that require treatment.

The uncertainty about the impact of hematopoietic stem cell transplant and enzyme replacement therapy, and that was the actually the genesis of my comment to you earlier, Coleen, about the -- my suggestion for the long-term follow-up

subcommittee, and looking at what happens to people who are transplanted. And certainly there's a Krabbe experience in New York where -- certainly for outcomes, but also for the concept of acceptability by parents for these kinds of treatments for non -- and certainly, you know, there are -- because Krabbe, there's SCID, which is a different -- I think I would say a different paradigm, you know, for other non-oncologic disorders.

There's uncertainty about the impact on the State laboratory and program challenges, and the public health impact, which will be, as I understand, now addressed formally by the evidence review group.

So I invite comments and, please, certainly from the workgroup -- Joe, Andrea, and others -- and questions. Thank you.

CHAIRMAN BOCCHINI: Well, thank you, Nancy, for a nice summary of the issues and the deliberations of the Nomination and Prioritization Committee.

So this is now open for discussion. Any

questions related to Nancy's presentation and the recommendation by the committee? Steve?

DR. MCDONOUGH: Yes. I'd like to move this forward to the evidence review. Make a motion.

I have a child in my practice with type 1 mucopolysaccharidosis. And we've been doing -- she came into my practice about a year or two of age, and we've been doing enzyme replacement therapy for about 10 years.

The attenuated form actually is of severe chronic illness, so when you think about attenuated, don't think it's a mild condition whatsoever. And it would've been very nice to have recognized these because these children will get treatment, okay? Either it's going to be in that window when they're diagnosed to get the stem cell, or they're going to get the enzyme replacement therapy. So there's treatment available, and they're getting it. The question is, are we going to pick these kids up early enough to, you know, help them, or better than later?

Now as life works in mysterious ways, but

as I was flying out to here on Tuesday, the family came up. And it was MPS Awareness Day actually on Tuesday. Anyway, I'm just going to share this. It's a little booklet that actually talks about -- pass this around -- about what her life is that she wrote at age 11, and it's been illustrated. And you get a little feel for what the quality of her life is.

But anyway, I want to compliment the work of the Evidence Review. And I, you know, as a general pediatrician, a lot of these conditions, you know, I'll never see in my practice. But I can just tell you my own personal experience that the attenuated form is a nasty disease, and this child would've been better off if we had picked it up prior to birth.

I would like to move it forward for a vote.

CHAIRMAN BOCCHINI: Okay. So Dr. McDonough has a motion that this move forward to the evidence review group. Is there a second for that?

DR. BOYLE: Can I just have some

discussion first? Would that be okay?

CHAIRMAN BOCCHINI: Okay. Well, yes. But I thought that we would either second that motion and then have a discussion before -- if there's -- by rule I think we have to decide about a second first. So, Charlie Homer seconds that. So now we have a discussion. Coleen?

DR. BOYLE: Just so -- and this has nothing to do with moving it forward or not moving it forward, but just clarity for me. So I was thinking -- still thinking about some of your previous slides when you went through the clinical utility slide. And so is there a good way to identify children with the early versus the later onset? You know, can we parce that well?

DR. GREEN: That's an important question. Dieter, do you want to take that question, or should I struggle with it?

(Laughter.)

DR. BOYLE: And, you know, this could be something that the Evidence Based Review eliminates for us, but I just want to know that for myself.

DR. MATERN: I think based on the enzyme assay or enzyme activity level, you cannot say whether it is early or late onset. There appears to be some genotype/phenotype correlation. In our study, where we tested more than 25,000 blind samples against, we cannot go back and ask anyone about addition specimens.

We did 20 molecular testing to confirm whether our enzyme assay or approaching concentration is consistent with MPS I. And we found four cases that have two mutations. And then in discussing it with John Hopgood who's in Australia and is one of the gurus in mucopolysaccharidosis, I tried to find out, well, what kind of mutations are these, and what can we expect? And he said, well, there's two I'm sure are severe, and the other two probably not, but I don't know. So that is my hearsay that I can provide.

CHAIRMAN BOCCHINI: Carol.

DR. GREENE: So clinician, and I see these kids, and with the caveat that in any disorder where there's a spectrum, there are going to be a few

people who sort of hit the gray zone in the middle. The answer is — just give me the kid and I'll tell you, okay, by exam. Yeah.

I mean, if you see a child and there's, you know, unusual -- I can't necessarily tell you whether there's going to be sparing of the central nervous system. But I can tell you by looking at a child and by doing a couple of X-rays, have you already got symptoms?

So the clinical spectrum of severe versus not severe is defined by, I don't know 50 or 60 years of clinical care of patients, and that's how we define them is by looking at them. So the answer is, yeah, I'm not going to say that we can do it. And Beth also sees kids, so she clearly is going to have something to add. But just a couple of other things.

So there are going to be people in the middle that are going to be gray zones, but, yes. We can tell if somebody is on the clinically severe side, we can't promise that they won't have CNS -- that they will necessarily have CNS problems.

I think we also need to say you can have two mutations and be not affected because if you don't have the parents or you don't do some other kinds of testing, you don't know if those are in cysts. So you can have two severe mutations in the same gene and the other gene could be normal. And that is going to come back when we talk about the definitions of cases.

We already said you can have zero mutations and be affected. And just for the record, there was a beautiful discussion of all the DNA diagnostic issues, but the clinical -- that makes it sound like the diagnosis is a lot more complicated and a lot more iffy than your mucopolysaccharides, and exam, an X-rays, and an enzyme assay.

And we have clear diagnostic criteria for this disorder, and the DNA is beautiful. It can be attached as part of the newborn screening, as a second tier test within the newborn screening. It can be helpful like with anything else. But there are clinical diagnostic criteria, and they're clear, and we can examine a child.

CHAIRMAN BOCCHINI: I think Beth and then Coleen. Did you just want to just follow up on that? Sure.

DR. BOYLE: So, Carol, I appreciate that, and I'm a long way from being a clinician. I was just trying to think within the context of newborn screening and really discovering children you'd never see perhaps clinically, you know, how you would make the distinction between an early and attenuated, if I'm following the language well, and so all those complexities.

Obviously you see children who are, I assume, for the most part, symptomatic, a little older perhaps in their course. So I'm trying to back off of that perspective of it.

DR. GREENE: The parents of the severely -- - of the classic early presentation kind, they were probably noticing an unusual sort of a little gibbus formation, an unusual shape of the back, and pointing it out it out to the pediatrician by one or two, maybe three months of age. You can tell on physical examination early.

And so I really appreciated your question because I think we were really focused on an anonymous population screen, and I think we need to highlight the fact that there is often late diagnosis. Now the later onset form, people may never get diagnosed. And some of those are the folks that could benefit from treatment the most so that they don't present in heart failure and arthritis the attenuated -- the later onset form.

But the early onset form, they will come to present because they will become very obvious. But they will be later in their treatment. But I just wanted to be really clear, there's very clear clinical presentation, clinical diagnosis, and criteria.

DR. GREEN: So, Carol, these are very helpful comments. Thank you.

I think maybe we should consider not using the term "attenuated," but really "later onset," because then -- otherwise it's potentially a distortion of the severity of the condition.

DR. TARINI: A few comments and a request.

So I agree and acknowledge with Dr. Green that there will be a gray zone in the diagnosis, and all diagnoses or most diagnoses will see a gray zone. I think the problem here is that where you sit, whether you sit in the gray zone or in severe, the decision that rests on that is a stem cell transplant. And so in some ways that ups the ante for the need for clarity on the diagnostic spectrum.

You know, in some cases when we have diagnostic dilemmas after the case of a positive screen, following them in clinic can cause -- requires resources, follow-up, maybe a burden to some degree to the family and/or the physician. But it is not a stem cell transplant.

And so one question I have is, am I hearing correctly that the physical exam, we are confident enough to rely on it, and that we'd use it as a judgment for sending a child to stem cell transplant, number one. And then, number two, as this moves forward -- I have no problem with it moving forward -- I urge, even if there -- let's say we have a window of time and we say, well, the

clinical exam for diagnosis is equivocal, and so the children need to be followed. In the Krabbe experience, we have evidence that sometimes these children don't come back to follow up. And so we have children who screen positive that are lost. And so we are losing a resource. We're losing the patients. And we don't know what happens to them.

So in addition, for the committee to also look at the long-term process of screening and how that has impact on resource utilization if these children are lost to follow up in their diagnostic period.

CHAIRMAN BOCCHINI: And that's an important point. First Coleen, and then Carol.

DR. BOYLE: I'm actually bringing in a whole new topic.

CHAIRMAN BOCCHINI: Oh. Well, let's finish this topic then, and then we'll go. Okay, so Carol and then Dieter.

DR. GREENE: So thank you. And I don't want to oversimplify. On physical exam you can definitely tell if somebody already has systemic.

What you cannot tell, and this will be relevant to the question of stem cell transplant, is there are very few people who have significant systemic presentation early, but seem to not have any CNS abnormalities. And those people you'd want to treat with ERT is my understanding.

And I do think that there is a window of time to watch, but I don't want to imply that there are no questions to be asked. But I do want to be really clear that it's not just based on the DNA, that physical examination, biochemical testing, urine MPS X-rays, have a very helpful role in here. But there will still be some in the gray zone.

CHAIRMAN BOCCHINI: Dieter?

DR. MATERN: I think assuming this goes forward to the Evidence Review Group, that group should really in their discussions with Washington State, for example, discuss the issue of the cases with no mutations identified. And then put it in relation to centers that do transplantations and enzyme replacement therapy, and actually figure out how many of those patients that receive treatment

because they were diagnosed clinically actually have no mutations, but enzyme deficiency. And I would assume that you will find very few that don't have at least mutation and got that kind of treatment.

So basically the question, these two without a mutation, are those actual pseudo-deficiency ones? And I know we state here that it's rare, but as newborn screening has shown us in the past what we think rare right now might not be so rare in the future. But since there might be specific mutations associated with pseudo-deficiency, it might be possible to figure those out quickly before actually reporting it out and doing a second tier molecular test.

CHAIRMAN BOCCHINI: That's a good point, and obviously with newborn screening, the focus on physical exam and other findings is going to be in the neonatal period rather than one month out, two month, or later. And so those are important comments. Nancy?

DR. GREEN: And just to build on that certainly, at least in New York for Krabbe, the

State convened all the State experts. There was more than one. And they came up with an algorithm actually for clinically evaluating children, you know, periodically in a structured way. Beth, your comments about loss during that time are very important.

But at the same time, I think that one of the messages to the Evidence Review could be that there needs to be structured clinical follow-up to help parce out what type of MPS I a child will have. That ought to be part of the algorithm.

CHAIRMAN BOCCHINI: Questions or comments? Oh, Coleen.

DR. BOYLE: So one relating back to what Sara mentioned in terms of the reconfiguring of the Nomination and Prioritization form. Well, I guess it's a nomination form. And the fact that there has to be a prospective population they study as part of that.

So you didn't point out whether there was one. You did talk about the analytic validity, but you didn't talk about the -- so there may be from

other countries, but I didn't see it there.

DR. GREEN: Thank you for that question. You know, for all of these disorders, it's such a moving target that if you just go to the published literature, you often miss it. So I'm going to open that question to those who would know. Sara, do you want to --

DR. COPELAND: Washington State -- I think that Washington State's blinded pilot will qualify as a prospective pilot.

DR. GREEN: And I guess we'd have to talk about that as a committee. I would not consider that to be -- you know, that's an anonymized sample, so we really can't make the decisions there. So I don't know. I mean, that's just my thoughts on that, but obviously that needs to be a committee discussion.

DR. MATERN: I think coming from a State -- well, from Minnesota, doing it any other way but blinded is going to be impossible.

CHAIRMAN BOCCHINI: All right. Steve?

DR. MCDONOUGH: With this condition,

there's been an ongoing registry for many, many years. And there's -- so as far as conditions go, as far as treatment and follow-up, there's a tremendous amount of data that's available for this condition.

CHAIRMAN BOCCHINI: Are there additional questions or comments?

DR. PARISI: I have a question about, although the attenuated or later onset forms the standard treatment is enzyme replacement therapy, is there any published literature about the use of stem cell transplantation in that population and what were the results?

DR. MCDONOUGH: Yes. Well, I'm not an expert on this, but I did read the articles on the way out on the plane. I think there had been 400 or so stem cell -- there's been more than 100 stem cell transplants, and there's been lots of enzyme replacement therapy as well. And then the reference article from a year or two ago talked about that.

I think the mortality rate for this 10 to 15 percent, and then there's only about half of

them, I think 53 percent actually the stem cell will take place, and you actually get a good effect. And then there's in between dying and having a -- well, I shouldn't say cure, but much improvement. There's between 10 to 15 percent, and that 53 percent there, partial takes or there's complications. So there is published data. And then the registry has excellent data on the effectiveness of stem cell.

CHAIRMAN BOCCHINI: Don?

DR. BAILEY: So, Carol, I'm inclined to support moving this forward, but I noticed that in the last slide you say that uncertainty is of public health impact. And my recollection is at our last meeting, we did not accept a condition to move forward because there had been no documented public health impact. And I just wanted to make sure I understand how we're applying that criteria, and are we doing that consistently, and we really all understand what that means. To me, I don't fully understand yet. I understand public health impact at a general level, but I don't understand yet how we're applying that at the multiple stages of our

decision process.

CHAIRMAN BOCCHINI: Yeah. That will be applied as part of the evidence review. There will be a need for public health impact as part of evidence review, and that will be part of our final decision about whether to accept something to be added to the RUSP, a condition to be added to the RUSP. But at this point in time, it's not one of the criteria for moving it forward to the Evidence Review Committee.

If we can go back to the criteria that are there -- well, no. I think stay with the slide that you had, I'm sorry. The major things are establish case definition, severe disease with serious outcome, evidence that there is a screening and diagnostic protocol, and then there is treatment intervention that may be or is beneficial. So those would be some of the key components that would then lead you to consider whether there's enough evidence for review, and that would include pilot study data and evidence that -- into a State laboratory function.

So I think those are the major criteria that are utilized to determine whether it goes to evidence review. And so it did meet those criteria with reservations that were brought forward by the committee. Does that answer your question?

DR. BAILEY: Maybe I'm mis-remembering. Last time I thought we were reviewing a condition last time to go denomination -- I mean, to go to Evidence Review, but I'm mis-remembering it. And we decided it wouldn't go to Evidence Review because of that. But, like I said, maybe I'm mis-remembering.

CHAIRMAN BOCCHINI: Yeah. I think it was it didn't go -- there were a number of deficits, but I think the key one was there had been no pilot study.

DR. BAILEY: Right.

CHAIRMAN BOCCHINI: Okay. Are there additional questions, comments? Do you want to make a comment?

MR. MILIEU: Hi. My name is Joseph Milieu. I just wanted to sort of add to all this. My son actually had MPS I. He was diagnosed very

early, six months old, by a very good pediatrician who picked up on it, diagnosed him. He went to Hopkins, got ERT first, and was treated with that for about six months, and then had a stem cell transplant.

Unfortunately he passed away. The stem cell transplant had complications. But the early diagnosis was very important because they diagnosed him early, and a lot of it was because of the muscular problems he was having. He was having -- I forget what you called it, but the problems with his wrist where his hands were sort of a little crumpled. And we were picking up a variety of things that just didn't seem right. Fortunately our pediatrician picked up on it. We went to a geneticist, who then sort of diagnosed him. But a lot of the early testing we found was all clinical. It was all diagnostics based on muscular problems.

To touch on the severity, he was tested for the enzyme and had zero function, so he had the most severe case. So it was picked up from that as well.

So I think, you know, just to comment on the early detection, I think it is really important. He was treated with ERT, and we did notice a change. He was actually doing better. But then he had the stem cell transplant, and unfortunately everything went south. But the ERT definitely did help, and I think that may be an interesting combination to do ERT first while you're waiting for a stem cell transplant or deciding if you need it or not because it does make a change, and it does help the child.

So I just wanted to add that from sort of a parent who's been through this.

CHAIRMAN BOCCHINI: Thank you for your comments.

Well, if there are no further questions or comments, we have a motion that's been seconded to move this condition to Evidence Review. So now we will vote. And to vote yes, we'll move it forward. To vote no, we'll vote against that. And I think we're going to go --

Okay. So the first question is, will

anybody choose to abstain from the vote? Dieter?

DR. MATERN: I will abstain since I was listed as a supporter or something like that.

CHAIRMAN BOCCHINI: Okay, thank you. Anybody else will abstain?

(No response.)

CHAIRMAN BOCCHINI: If not, we're going to do an alphabetical roll call. I'm going to start at the top, Don. So, Don Bailey.

DR. BAILEY: Whatever the right -- yes, I agree. Yes.

(Laughter.)

CHAIRMAN BOCCHINI: Okay. Yes or no. Okay.

Bocchini, yes.

Coleen Boyle?

DR. BOYLE: Yes.

CHAIRMAN BOCCHINI: Denise Dougherty?

DR. DOUGHERTY: Yes.

CHAIRMAN BOCCHINI: Charles Homer?

DR. HOMER: Yes.

CHAIRMAN BOCCHINI: Kellie Kelm?

DR. KELM: Yes.

CHAIRMAN BOCCHINI: And Fred is absent, and Dr. Lu. Michael Lu?

DR. LU: Yes.

CHAIRMAN BOCCHINI: Steve McDonough?

DR. MCDONOUGH: Aye.

CHAIRMAN BOCCHINI: Melissa Parisi?

DR. PARISI: Yes.

CHAIRMAN BOCCHINI: Alexis Thompson?

DR. THOMPSON: Yes.

CHAIRMAN BOCCHINI: And Andrea Williams.

MS. WILLIAMS: Yes.

CHAIRMAN BOCCHINI: Thank you. This will move forward with unanimous vote yes with one abstain. Thank you. So thank you very much.

Now we will break for lunch. We will return at 1:00 p.m. promptly to begin the deliberations for the second nominated condition. Thank you.

(Luncheon recess.)