Transcript: February 1

Event ID: 2098082
Event Started: 2/1/2013 9:25:16 AM ET

Good morning everyone, this is Sara. Our fearless leader is on his way. He's a little indisposed this morning, is moving slowly, so I thought I would at least go through in trying to take roll call, if that's okay. Don Bailey?

Here.

Jeff Botkin?

Here. Carla?

I'm here.

Denise Dougherty

I'm here.

Wonderful, and Alan and Melissa this morning?

Alan is here.

I'm here.

I'm here until a little bit before noon.

Kelly?

I'm here. Dr. Lou?

Steve McDonough?

Here.

He thought he might be a little bit late.

Cathy Wicklund?

And Andrea Williams, are you here yet?

I'm here, here.

[Indiscernible - poor audio]

Nancy Rose? Lisa Bujno?

Here.

Good morning, how do you pronounce your last name so I do it right?

It’s pronounced boy-no --

Susan?

I'm here. Chris?

Here.

Good morning. Were you able to get onto the webinar today?

Yeah, I am.

Excellent.

Again, I think it's our issue so we're working out here.

Is Theresa Hart or Barry Cohen for DOD?

Theresa Hart, here.

Natasha Bonhomme?

I’m here.

Ed McCabe?

Here.

I’m sorry, did you say “here”?

Yes, sorry, I was unmuting.

Cate Walsh Vockley?

I'm here.

Carol Green?

Good morning and thank you guys for hanging in there. We are -- we have a shortened day today. Lisa, can you pull up the agenda for me please?

Do you see the agenda?

I think so. I'm going to go through some housekeeping notes so we can get things started [indiscernible - multiple speakers]

Hey Sara?

Yes ma'am.

There's a little bit of feedback. I think someone's computer speakers and phone line are interfering with each other --

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Turn off any computer speakers for the members and Org Reps.

The operator can also mute their lines probably

The operator can mute the lines.

Did you want me to just close all lines at this point?

Just except for me.

Okay. All lines are muted.

Excellent. So I'm going to go to the housekeeping notes. It's probably not really necessary since we have the wonderful operator that can turn your noise off, but I'll go through it anyway. Sound for Committee members will be coming through your phone line, so please make sure you have your computer speakers turned off. Even if you are muted, it can cause feedback. Hold questions and comments until the each of presentation, press star one for questions or comments. When invited to speak, say your name each time and I will try to remember to do that as well. To ensure proper recording for the committee transcript of minutes, then press star zero if you have any problems with your phone line. Members of the public, sound will be coming on through your computer speakers, so please make sure you have your computer speakers turned on. Hold questions until the end of each presentation, and I'm going to try and remember this time to ask Lisa to put up the chat box at the end of each presentation so you can type in your questions if you have them. Please remember, everybody can see what you type, and so you probably want to be discreet. If you are chatting with other people online, you probably want to make sure you're not sending it to everyone. To ask a question, go to the lower portion of the chat box and type your question, then press the send icon. Okay, so done the roll call. Is Marci on the line's Marci, if you're here please press star one on your phone and inform the operator to open your phone line Marci? Are you on?

Marci your line is open.

Thank you, I am here.

And Amy we might as well get your phone line open as well. Amy can you press star one?

Okay Amy and Marci remember that your phone lines are open so remember if you're not speaking for yourself unmute. So I presume Marci you're starting?

I am.

Marci Sontag is an Assistant Professor of Epidemiology and Pediatrics at the Colorado School of Public Health and the University of Colorado Medical Center. She has a PhD in Epidemiology and an MS in Biometrics from the University of Colorado Health Sciences Center. Dr. Sontag has studied clinical outcomes and newborn screening in cystic fibrosis since 1995. Her research in CF has resulted in a better understanding of longitudinal progression of pancreatic damage and a new algorithm for CF newborn screening. Dr. Sontag is helping to lead the efforts to implement CCHD newborn screening in Colorado and working on a pilot study of Spinal Muscular Atrophy Newborn Screening. She is also Director of Epidemiology at the Newborn Screening Technical assistance center. Amy Brower, PhD, works on several projects at the American College of Medical Genetics including serving as Project Manager on the National Coordinating Center's Long Term Follow-Up Project and as a team member of the Newborn Screening Translational Research Network. Dr. Brower also works with Aurora healthcare and she has a background in medical genetics economics and -- member of the human genome project team. Dr. Brower is a former member of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and is a consultant to the follow up and treatment subcommittee and a member of the health information technology worker. Thank you so much. Marci, you can go ahead and get started.

Thank you very much, and I'd like to thank the committee for allowing us this opportunity to update you on newborn screening, then Amy will follow with the implementation status [Indiscernible - poor audio] new disorders -- this while this can do CCHD was added to the recommended uniform screening panel in September of 2011. And the one following that recommendation, HRSA funded six demonstration projects across the country in five states and one region of the Northeast to implement newborn screening is to share best practices with each other and the rest of the country. This is six states many other states are working towards implementing CCHD for newborn screening and already performing screening in their states. However, in that approach limitation is buried, so I'm going to try to give you an idea of what is happening across the state through this presentation. So we'd like to talk today about the current status of CCHD screening and legislative needs across the states, and the progress states are making, talk about the pilot studies and local of the mentation efforts of those dates the many challenges and barriers to CCHD screening and how we are helping states to overcome some of those barriers. We'll also talk about some of the data collection efforts that are going on nationally and at local levels, and the next step -- [indiscernible - low volume] -- today comes from three places, the newborn coalition, who is an advocacy group that really helps to be the policy development process when needed. However, it is a big task to keep up-to-date with all of that information, so we have fabulous online

map to access to get that update but, we are going to be working with them to have a vital and keep those maps of today. [indiscernible - low volume] the surveys since January from states, asking them what the status was and what the legislative up-to-date across the states, we have a little bit more information. We reach out to the HRSA-funded regional genetics collaboratives to assist us in getting the rest of that information. The legislative process, we received survey results from 40 states, adding new conditions does vary by state. As you might imagine, of the 43 states that responded, 23 of them said legislative action was required in the state to [indiscernible - low volume]. However, in 20 states specific legislative action is absolutely necessary, but we could pursue that avenue. However, we could also pursue the Board of Health advisory committee, the Commissioner of Health, different process existed in each state but it's something that's outside of that legislative process. We have evidence that legislation has been introduced in 29 of the 50 states. On the next slide I'll be showing -- in addition to those states, currently active legislation is pending in 10 state. Among the states that haven't passed it or currently considering, those connotations have been awaiting more information. Best note on these two of 29 states that legislation has been introduced there's funding mentioned in the [Indiscernible - poor audio] -- first these are maps provided by the newborn coalition and the maps are multi colored and have interactive map so you can get it more permission on additional states we like information. This legislative map shows the darkest states. The darkest gray, that's where legislation is passed. The lighter gray states are those where legislation has been introduced, in the white states are states where formal legislation has not been introduced yet. I have, for the purposes of the presentation this morning, added yellow stars -- 12 the states where legislation has been passed.

Many of those states have implemented CCHD screening, moving forward legislation recently passed in the process of formal implementation of CCHD tools. We mentioned earlier there are several states that do not need legislative mandates, and states have successfully passed CCHD screening through avenues other than legislation are represented here by the screen stars. So another four states have implemented CCHD -- that does not imply that those dates represented on the legislative mandate on the legislative side previously, that was the mechanism by which it was approved in their states. Here's the slide indicating where states [indiscernible - low volume] changing landscape, Heart Association introduced bills in states and working with the newborn coalition [Indiscernible - poor audio] in addition to that many state newborn screening committees are actively involved -- topic of conversation was most of the state advisory committees -- these are the states that reported back to us in our surveys that they are actually considering it and moving forward with efforts to implement CCHD newborn screening. And then we asked the question, what else is going on in your state, localized screening and you can see that across the country there are many states reporting back to us that there are active studies or local hospitals implementing CCHD -- but gray states and I suspect there are actually other states participating or hospitals are participating in CCHD screening of very careful [Indiscernible - poor audio] the Secretary's recommendations and implementing that as possible locally it might be that the local state health departments don't know about that, yet communication has been opened but I suspect there's even more states that includes hospitals -- local CCHD screening -- and finally, map of the HRSA-funded pilot demonstration projects. As I said earlier, there are five states and the rest are in the Northeast, a little bit bigger than the others because that is collaboration across several states in New York -- we take these maps, overlay them, we see that there is a lot of CCHD activity going on around the country, from legislative or other mandates to states doing pilot projects and demonstration projects. So the next question you might ask is, how do we get all of these states

with those multi colors to be green or orange, representing states who are actively implementing CCHD screening. We ask the states what are the challenges and barriers to implement CCHD and the first one, among public-health avenues, is funding. The biggest funding challenge is setting up that data system, setting up the data system within public health, to correct the data and development of that surveillance system, and then there's also the challenges of convincing public-health decision makers about the algorithm of how we're going to do this -- and other resources -- more details on that. Figures are showing the challenges and barriers to implementation. They could check as many answers here is they wanted so -- adding up to more than 100. Funding was one of the biggest, and time and resources -- in part funding and in part setting up a time to do it -- you notice that the current resources -- bigger [indiscernible - low volume] public-health decision makers, hospitals and clinicians -- almost 50%, and challenges with the screening algorithm, and we looked at an example of -- and whether we do have an algorithm, to concerns other than implementation -- [Indiscernible - poor audio] how we would expect to legislate attitude challenges -- then we asked about the timing of implementation and this is somewhat similar to the data that Jelili presented yesterday about Pompe screening and implementation -- how long does it take to process to reach a decision? We found that a few states can do this in less than six months. In the majority of state, are either between six months and the year, or more than one year but less than two years. A few states that said this is going to take us at least three years at this point. All the screening conditions but I'm not entirely sure that [indiscernible - low volume] one of our goals is to help -- what is that minimal data set for collection, what should states be collecting for CCHD newborn screening, both locally and what nationally? Really the first question we need to ask here is, what is the role of public health in CCHD screening? So I think you can all agree public-health gets involved in quality assurance, surveillance, quality improvement when it comes to CCHD screening, but does it really look like and how are we going to implement that one of the resources, where they are going to be involved, what is HRSA – [indiscernible - low volume] types of data to be select -- discussing -- different approaches to testing was done or not done on an aggregate level in those hospitals for those babies -- data on babies who fail the screening, or all data on all screens. As an Epidemiologist, I would like to request all data on all screens. However, there a lot of resources involved, we'll talk about on the next slide. But in order to really be able to think through these issues, many national partners are joining together to help with these efforts. So partners and incentives for disease control and ship the -- National Library of Medicine, the American College of Medical Genetics, and is Steve -- we are [Indiscernible - poor audio] working to develop and modify an existing systems. We had some discussion about this yesterday at the Follow-up and Treatment Subcommittee meeting -- modify early kinds of detection and intervention systems that are already in place, modify and link electronic birth records, there are commercial systems that are available that if you have [indiscernible - low volume] to the hospital into the public-health system and looking at developing new data collection systems. New steps is developing a national newborn screening repository on a national level, on babies with disorders identified by the screenings, and we also develop quality indicators to track metrics and state newborn screening programs, and this is through CCHD screening. So finally what are the current resources for states, and next steps, in moving forward with CCHD training. We are having monthly webinars timely topics, focus and basic levels. These are on alternating months, and monthly events where states can come together, and share ideas and resources and challenges. The National Children's Medical Center has an online resource, there's a link there that has a lot of information for CCHD screening, there's a listserv by HRSA to pose questions and offer solutions. That has been great, to share information and questions about CCHD screening and identify

resources and partners to assist dates, and looking forward, to develop resources for the states, as we are in conversation with them and other readers. Before I take questions, I'm going to hand the podium over to Dr. Amy Brower, who will be giving you similar updates on screening and implementation.

Hello, everyone I'm Dr. Amy Brower, thank you for the opportunity to give you an update today on the implementation of newborn screening for Severe Combined Immunodeficiency. The purpose of the report today is to update you on activities across the nation and across the stakeholder groups. As you know, Severe Combined Immunodeficiency has been the topic of discussion at the Secretary's Advisory Committee meeting really from the inaugural meeting in 2005. For decades ago as you know, really the clinical case in the bubble boy disease that many people link to Severe Combined Immunodeficiency all away over the last several years as newborn screening has been implemented and operationalized across the state programs and with the American College of Medical Genetics and genomics and clinical implementation of Severe Combined Immunodeficiency (SCID) screening. We talked in -- to provide an update to the Secretary's Advisory Committee, and screening for SCID represents the largest expansion of newborn screening since the advent of tandem mass spectrometry over a decade ago and the Recommended Uniform Screening Panel (RUSP) five years ago. Because SCID screening is a molecular test a little bit different than CCHD, the doctors talked about, state newborn screening programs that had -- expertise in or and sharing existing regional expertise to implement screening for SCID because we look across his timeline, beginning with the workshop organized by the Centers for Disease Control and Prevention (CDC) in November 2001, to begin to discuss ways to improve outcome for patients with primary immunodeficiency disease all the way through in 2005. The discovery at NIH by Dr. Chan and on a way to diagnose newborns with SCID in newborn screening samples, all the way through many different activities in 2006, these availability of QA materials from CDC groups the state piles, beginning with Wisconsin, and then the expansion rapidly by NIH and then NICHD in 2010 to expand the number of babies that were screened through the addition of -- through the RUSP newborn screening training programs in 2011 that began, posted by HTL, CDC, other partners all the way through implementation. Now, a laboratory guy from the Clinical Laboratory Standards Institute (CLSI) will be available this spring, so the talk today was really designed to talk about implementation. Beginning with Dr. Rebecca Buckley at the marble meeting in 2005, advocating for newborn screening for SCID, and then several visits by Dr. Jennifer Puck and Dr. Buckley across the years, they were going to focus on implementation. So let's see what's been happening since 2011. So it's been three years since the Secretary's Advisory Committee's recommendations to the RUSP. We see that implementation has expanded across the United States. We currently have 12 states that are screening for SCID; this represents over 40% of newborns. We've now received an initial screen for SCID, there are some states that some populations have selected screening. In Arizona and New Mexico, you see their selected screening of the Navajo population, and in Pennsylvania, so it sort of has the hashmark and that we have several states that are very active and have big plans for this year in 2013, as they begin pilots or statewide screening. There are 14 states that are beginning that in 2013. We estimate that the it -- at the end of 2014, all of these states are screening will be about 60% of newborns that will receive an initial screening for SCID. The states marked "no screening" there that doesn't mean they're not busy and active. As Marci said, about 40% of states require legislation to expand the conditions that are screened in their states, so those dates are very active. They just have not yet implemented newborn screening for SCID. So were we look at it the implementation status really

beginning a walk through history and starting now with Wisconsin, which began statewide screening in January 2008, this is just to really let us know the number of babies that have received screening today, followed by Massachusetts who began and shortly after that in February of 2009, and then the Navajo nation as a target population because of the higher incidence of SCID. This represented about 4% of newborns across the United States, as we reported to the secretary, no cases of toxic SCID were found in the initial years of the screening, so NIH stepped in and rapidly expanded the screening by doing a pilot in California and New York, and Puerto Rico. So these are some totals from California, 420,000 babies were screened as part of the NICHD pilot, and that pilot screening has continued in New York, and we see 168,000 almost were screened during the pilot and that has continued, and then in Louisiana and Puerto Rico both of those dates utilized Wisconsin and Massachusetts in a regional innovation screening, where they actually sent the dried blood spots to the states Wisconsin and Massachusetts, and they performed the screening for that. Those dates are now great because they're not actively screening once the pilot was completed. But since the pile was completed, several states have now added screening ports combined immunodeficiency including Michigan, Connecticut, Colorado, Mississippi, Delaware, Florida, Texas, and recently, in January just a few weeks ago, Minnesota. All of the states together represent about 3 million babies screened today, or SCID. That means a lot of positive cases, fear learning a lot about the trajectory of the types of conditions that are identified by the -- learning a lot about immunology in immunology disorders in the newborn. So some selected statistics today, the total number of newborns that have been screened by the end of last year was about 2.85 million. This represents about 45% of births screened in the United States. There are 12 states that are planning on pilots or beginning statewide screening in 2013, if all of these states implement and no other states these decided jumping, there's about 62% of births by the end of 2013 that will be screened for SCID. We also post monthly calls for stakeholders, and advocates join those calls. We do understand that there are 15 cases of SCID, classic SCID, that have been diagnosed in states that are non-screening. Of those 15, it's a 60% of those babies are still alive. So there are several resources for newborn screening laboratories that are available through the CDC in through NICHD, and going efforts by and does continue to report the adoption of SCID newborn screening, including technical assistance, publication of pilot results, screening and best creation of data sets to determine impact of screening on health outcomes, and expert working groups to continue to refine screening diagnosis and treatment protocols and guidelines. CDC also is funding more demonstration projects on newborn screening. So specifically, CDC has been part of an effort to create a CLS I guidance document. The development of this document -- the chair holder is Dr. Gary Chanan, in the vice chair holders Dr. Rashidi Abraham from the Mayo Clinic, we expect this guidance document, which really covers the gamut of information that you would need to have to implement newborn screening for SCID, all the way from the protocols and the algorithms in the technology through short and long-term follow-up, will be available this spring. As I said, CDC also has two active cooperative agreements which look at statewide screening in the states of Michigan and Minnesota that are active. Another tool that is available for the states is a SCID module. This is a module, that is a database, that really facilitates analytical validation of screening. As we've said, the molecular, this is with the screening, it's really the first time that a molecular method has been the first tier screening newborn screening level. So this is really a way for states to aggregate and share information and what they're learning as they develop and implement this new molecular tool. We also added in clinical information, so it does include condition type, six different categories and conditions so for cytometry, so this is supposed to help us as we understand more about the screening and how it remains to immunodeficiency. The cooperators of

this good module is hosted at Mayo and AC Mgr, Dr. Rashidi Abraham and Dr. Fred Lorey from the California newborn screening program. There are several other groups who have put his resources for healthcare providers, and a focus on short and long-term follow-up person, a CMG, have supported clinical decision and support materials are called action sheets that are available online, and new newborn screening toolkits for advocates, so they help with the implementation of screening and states will produce some pamphlets and peer education material. CDC, APHL, and Jeffrey Modell foundation, along with two-year fellowships for postdoctoral candidates and newborn screening research, including immune deficiencies. The Immune Deficiency Foundation, which joins our monthly calls and gives us updates, have created educational resources for families and states because of the Internet and the wide sort of knowledge of what happens at the Secretary's Advisory Committee, we often get calls from parents and this is a way to put parents and families and advocates, together with experts, and share information and for those parents and advocates to funnel their energy into helping those legislative and other activities in individual states. We also have several resources for newborn screening. Researchers at the NICHD in the NBS DRM, these include the website that has a report of the national SCID pilot study. In that report, the national SCID pilot study includes the laboratory protocols and the short and long-term follow-up protocols that were operationalized in that landmark study. We also have a NBSTRN virtual guidebook repository, which includes several thousand characterized samples for SCID, and we now have the longitudinal pediatric data resource, which is available for clinicians and researchers and public health partners to use in collecting information on screened positive and diagnosed cases. These are all available, and diagnosed cases. These are all available at the NBSTRN.org website. As we know, we talked a lot about a few years ago, about the rapid expansion that was provided by the NICHD-funded study, read by Dr. Michelle Caganna from New York State. As we know, that increase of percentage of babies that were screened, from 4% to over 25% in the six months prior pilot, rapidly identified several cases of classic SCID. We spoke in May of 2011 about some of the early findings of that study, where we compared the New York and California classic cases of SCID in the racial or ethnic distribution with the retrospective study from our colleagues at Duke, and although the numbers were small, they were intriguing that we began to see that the cases that were identified at that time. The newborn screening, looking at ethnicity, differed significantly different from the race and ethnic categories that were reported in this new Duke retrospective study. So, to foster this type of research in this type of data collection, we now have the Longitudinal Pediatric Data Resource (LPDR) to create a longitudinal record of information as these newborns are screened and diagnosed all the way through their life force. This is just a sample of some of the information that we are enabling researchers and clinicians and public health partners to begin to collect on these cases of immune deficiency, so we can learn more about the trajectory of the cases that are being identified, and again this is some early data from California that points out the importance of in the heterogeneity of the different conditions that are being found by the assay. And this summaries California, pointing out that with newborn screening they haven't over 90% survival, and we hope that the LPD I will be used by the states across the board so we can understand the improvement in health outcomes for newborn screening for SCID. The NBSTRN is funded as contact to the American College of Medical Genetics, and from the Eunice Kennedy Shriver National Institute of Child Health and Human Development at the NIH. Thank you.

Let me thank both Amy and Marci for two excellent presentations, and we are open now for discussion or questions, and back to start with the members of the committee. So all the phone lines open?

Yes, all the lines are currently open and interactive.

The public can type in their questions into their chat box as well, which we will try to address, after the members have had their chance to ask questions.

Any questions from committee members?

[indiscernible - multiple speakers] This is Jeff I wanted to make a comment about Marci's presentation in particular. Just to highlight another barrier, and I don't think I'm speaking out of turn here, but Utah is one of the study sites – Secretary's Advisory Committee recommended research, additional research on this, and that's being conducted. You taught one of the sites in high-altitude site, try to better characterize post-oxygen -- screening data and data at altitude in the challenge, that the Utah has been experiencing this there would be approval for pilot study. So I think there's two levels of issues here. One is when can we characterize these pilot efforts as quality assurance and when are they researched, and secondarily what's the rule of permission for work in this area and the issue is not been set, basically the initial finding of the IRB, the health department IRB was that this needed to go forward -- both the hospitals were involved in the study approved a waiver of written consent. So I think this reflects a larger issue that I would like to have our Secretary's Advisory Committee check out in the future meeting, the Newborn Screening Transitional Network has a draft paper that's going to be coming out on the parental permission issues that tries to speak to some of this. But from my perspective, a barrier to the conduct of research and this domain, that I would like to recommend the Advisory Committee take up for some discussion.

Additional questions or comments?

This is Cathy, I got a question as well. Did you guys look at any other barriers as far as follow-up that would be necessary, because there were several things about implementation [indiscernible - multiple speakers] you guys also looked at [indiscernible - multiple speakers] pediatric cardiology availability or resistance to a provider or anything like that --

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Not -- access to it cardiology or cardiology clinic or a facility to travel -- like a cardiogram -- we did not assess specific question our survey. But you bring up a good point that we will keep in mind for future surveys --

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I would like, I think Sara knows about this as well, one of our students are graduate students in genetic counseling. This is Cathy by the way. When I had, and she did also, do a survey and she got responses from 45 states and she did look at them, that was just for comparison sake, and maybe what I'll do is have her contact you directly to talk a little bit more, because we did ask specifically about follow-up and Jeff we asked about informed consent, and general service written or oral, and two states out of the 22 that answered this question said that "yes" or would be informed consent

required. For CCHD. And 13 were “no” and then seven were not determined. Remember that survey? I would love to be contacted.

This is Dr. McDonough. Can I ask a question?

Yes, go ahead Steve.

Did you have any feeling or any information about the ability -- availability of health departments to screen for new conditions as the Advisory Committee recommends over the next couple years, as they deal with the SCID and this CCHD implementing, will it impact their ability to handle screening for new conditions?

This is -- thanks for that question, very timely. I think what we've seen with the implementation of SCID it really represented challenge and -- both a challenge and an opportunity for the state newborn screening programs. This is a first time that they would do a molecular test as a first-tier test, and I have to say that the states have responded very well, that they been able to share information that work with partners from NICHD and CDC to really gain the expertise to be able to do this type of a molecular test. As we know, with next-generation sequencing and other molecular events, molecular technologies being discussed in newborn screening series, and I think the capability across the state programs, although it varies, has been very good in implementing this type of an assay as a first-tier. We've also seen with their systems that they have in place, from advisory committees, to approach the legislation to producing material for parent and the primary care physicians, and the special is that they really have built systems. Although each state is a little bit different, there is a spread of commonality across the states, and I think that the HRSA-funded regional collaborative has really helped it coordinating those efforts. As you know, there are seven regional collaboratives across United States, and they share information and full expertise, and I think that has helped increase adding toolkits for the implementation of SCID across the state, so I think there are several models that the Secretary's Advisory Committee can look at, and could encourage states to continue to use and to help them, and broadening the expertise across the state. So I think it's gone really well although we hope we would wish we were at 100% of the state screening versus what could three years after the recommendation. A lot of progress has been made and a lot of learning has happened across the states.

Thank you for your comment. Other questions or comments?

Let's open it up to the --

This is Chris, and I actually typed it in but I think one of the issues and particularly the discussion about CCHD is the importance of, again, saying was the role of states public health but what's the role of federal public health. The example I gave is that, we in New York State, probably would be implementing CCHD screening if would've been a grant recipient. We weren't in, so now we are looking and I think it goes to Steve's point, looking at where do the resources come to implement it on the state level, given all the cuts that we've had and the shortage of funding.

Other questions comments? Once again thank you Dr. Sontag and Dr. Brower for the timely updates. Thank you, and we look forward to continuing to [indiscernible - low volume] additional -- thank you both.

Operator can you please mute all the lines?

Yes, one moment while I mute all lines. --

Next on the agenda is Dr. Urv on the sequencing the newborn screening initiatives. Dr. Urv is a program director of the Kennedy Shriver NICHD and -- you works in the intellectual development -- receiver of graduate degrees from [Indiscernible - poor audio]. Prior to joining the NIH, she was an assistant professor at the University of Massachusetts medical schools Eunice Kennedy Shriver Center, and research scientist in New York State Institute for Basic Research and Developmental Disabilities. Dr. Urv

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Hi this is Tiina. Can you hear me?

Yes we can.

Okay great. I'm here to talk about genomic sequencing in newborn screening disorders, and the initiative that we have that NICHD was in collaboration with the National Genome Research Institute (NHGRI), and I'm going to start by telling you this topic that I actually can't say a whole lot about, because we haven't started these projects yet and they haven't even been reviewed yet, but what I'm going to do is I'm going to give you a little background about how this all came about. So thank you all for being here today, and this initiative actually started as an idea that was stimulated by discussion of genomics that the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and this was actually Aliquippa Marker's idea. He came to me after one of the sessions and said we really need to look into this. And it was early 2010, and there's a great deal of talk about speed at which the field of genomics is moving, and then an illustration of the pace of this change in the field would be the human genome project that took 13 years and approximately $100 million to sequence one genome. If you fast-forward to 2010, at the time the estimated number of completed human genomes would be 2700, and predicted by the end of 2011 the number could be as high as 30,000 -- 10 times as many as the stick figures as you see on the slide. A number that I'm not sure, that the PowerPoint would've coped with in that impact, this slide almost blew up the slide deck when I was loading it. So the question that was brought up in the committee was how -- how will we see the seeming tidal wave of impact that public health programs, such as newborn screening, and prepare for these changes and the impact it might have on newborn screening and child health Alan Kumar care in their green, brought together staff members and the intention was really to organize a workshop to the steps to address these concerns. On December 13 of 2010, NICHD and NHGRI and the NIH Office of Rare Diseases Research sponsored research of newborn screening of the genomic area, setting a research agenda. The purpose of the meeting was to identify elements of the trans-NIH research agenda that would lead to the application of new genomic concepts and technologies to newborn screening and child health. The meeting was attended by experts from academia and industry and federal agencies in the field of newborn screening in genomics, and it was chaired by doctors from Johns Hopkins and the Mayo Clinic. The primary outcomes of the proceeding from that group was that it was

important to evaluate genomic data in newborns, using the newborn screening as a framework. Second, it was important to prioritize clinical validity and clinical utility, not just analytical validity, and finally it was important to address ethical legal and social concerns. And this sort of became our three-legged stool when we went forward in developing the initiative. So after the meeting, staff from NICHD and an NHGRI continue to collaborate, to develop an initiative to explore the implications, challenges and opportunities associated with the possible use of genomics-sequenced information in the newborn period. And our working question was really what can be done, and what is the value added of this information? We wanted to develop a model of how to thoughtfully explore these challenging issues related to these genomics in newborn screening. And we refined the three points from the earlier meeting into what we kept referring to as our three-legged stool and this became the foundation of the initiative. What I'd like to emphasize is that this time these projects, once funded, are intended to be pilots and we want them to produce, to start building a foundation of research that others can build upon and that can be used to make informed decisions. So first, we felt that it was important to give the investigators parameters that were focused on newborn screening, that we wanted each applicant to address one or more of the following questions. First, for disorders currently screened for in newborns, can a genomic sequencing replicator augment don't newborn screening results? Second what knowledge about conditions not currently screened for in newborns could genomic sequencing of newborns provide? And finally, what additional clinical information could be learned from genomic sequencing relevant to the clinical care of newborns? So it was compulsory that each of the projects that was submitted had it -- had three components. A genomic data set, clinical research, and ethical legal and social implications research. So for project one, which is the genomic dataset, we required that the -- collected genomic data set that expanded considerably the scale of data available for analysis in the newborn period. This component of the initiative required that the collection of analysis for each participant of a large genomic data set, and in the context of this project we defined it as meaning a collection of high quality nucleic acid data from all or a large portion of the genome of each of the study participants. At a minimum, the scale of data that required was a whole genome or whole [inaudible]. The second component was a clinical component and the research we were looking for will advance the understanding of specific disorders identified via newborn screening through promising new DNA-based analysis. In this component of the initiative focus on disorders that are currently identified by newborn screening or that could potentially benefit from early identification by newborn screening. Really again we were trying to narrow the parameters of the types of projects that were coming in. Possible research projects that we suggested were correlating genetic genomic and pharmacogenomic information with phenotypic data to determine prognostic factors in disease presentation, progression, and response to therapy for disorders identified to newborn screening; or identifying the relevance of genetic variants; or developing an analysis pipeline. Again, these are just suggestions that we gave to investigators. Finally, the research related third component is research related to the ethical, legal, and social applications the LC component of the possible implementation of genomic sequencing of newborns. This component of the initiative involves studies related to social -- social and when we say social we included the ethical, psychosocial, legal, and economic issues that may arise from the possible implementation of genomic sequencing of newborns. So one thing we really emphasize was that each of the sections needed, each section needed to be as strong as the other, so when the genomic datasets in the development of new technologies could not be any more important or valuable to this project in the clinical component and the ethical component, also needed to be a strong as the other two. That was something we really emphasized when we were

working with the investigators. We use the U19 mechanism, which is a cooperative agreement which -- uses substantial federal programmatic -- assist investigators during the performance of the research activities. It also allows us to bring all the investigators together from all the projects that are funded for discussion. The budgets and NICHD and NHGRI intent to commit an estimated total of $25 million in the application budget should not exceed a total cost of $1.25 million per year and must reflect actual needs of proposed research project. The scope of the proposed project should determine the project period. The maximum project would be five years. The important dates for the letters of intent came in October 19, the applications were due on November 19, and can't tell you how many applications came in. The review will be at the beginning of April. The earliest we will find out anything about how the review went was after the Advisory Council. NHGRI has their Advisory Council in May, we have ours in June. That means that the earliest start dates for these projects would be in July. This was really a team effort led by Alan Guttmacher and Eric Green, and on the NICHD was myself and Melissa Parisi and in NHGRI was Anastasia Wise, Jeff Schloss, Joy Boyer, Lucia Hindorff, Lu Wang, and Teri Manolio, and I had a great experience working together with them. So if you have a questions, I may or may not be able to answer them. Thank you.

Thank you very much for bringing us up to date. Questions from the committee? Let's open the lines

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All lines are open and active.

Thank you. Questions from committee members --

Were you going to ask a question?

As a reminder the public question chat boxes are open, so if anybody wants to type in a question, they can -- [inaudible - static]

All right, there's no questions from the committee, how about the -- any additional questions or comments?

Can I ask a question?

Sure.

This is Nancy Green. Good morning, thank you. Tiina, are those sequence data and algorithms, etc. all are publicly available? I assume under NIH policies, just asking --

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And it really depends on -- they are -- it depends on the regulations. For example, if they're working with the specific state data, some states don't allow information to be shared and we have to respect that. But we encourage as much sharing of information and data as possible. -- I think the limit is because there's some clinical information linked to the data and that would cause some concerns. So --

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Thanks.

Sure.

All right, additional questions or comments? I'd like to thank Dr. Urv for the update. I think this is very -- exciting project that's coming to fruition, and we will look forward to hearing what comes from the selection in the project center -- that are chosen -- thank you very much.

Operator, if you could please mute the line.

Okay, one moment. All lines are currently muted.

Next on the agenda we have Dr. Jerry Mendell. This is an update on MDA Muscle Disease -- newborn screening for Duchenne Muscular Dystrophy. He is a Professor of Neurology, Pediatrics and Pathology at the Ohio State University. He holds a Chair in Pediatric Research and is the Center Director for Gene Therapy at Nationwide Children's Hospital. He is also the Director of the Wellstone Muscular Dystrophy Cooperative Research Center. He graduated medical school from UT Southwestern, followed by neurology training at the Neurological Institute at Columbia University. He holds three INDs for gene therapy products taken to clinical trial for DMD, LGMD, and sIBM, and Becker muscular dystrophy. He has had multiple interactions with the FDA in pre-IND meetings preceding IND application. Dr. Mendell were pleased to have you here today

Before Dr. Mendell gets started I like to give some context to this presentation. Because this is not a request for addition to the RUSP at this point in time, I just wanted to point out that the Duchenne Muscular Dystrophy, there is another Secretary's Advisory Committee that is related to Muscular Dystrophy, and when they had this symposium last September, the Duchene Muscular Dystrophy Association asked to present the proceedings from that symposium. That is the purpose of this meeting, is to update on what was said at that symposium. Thank you.

Dr. Mendell?

Can you hear me?

Yes, we can.

Go ahead.

I want to thank the Secretary's Advisory Committee for the opportunity to discuss the status of newborn screening and Duchene Dystrophy. Trying to advance the slide here. Okay. In September 2012, the MDA held a symposium on newborn screening and Duchene Muscular Dystrophy. Individuals in attendance included those intimately related to newborn screening, experts and neuromuscular disease and molecular diagnostics, and representatives from patient advocacy groups, the CDC, and NIH. This slide shows the participants, many of the names will be familiar to you. The blue highlights are the people who spoke at the meeting. The objectives of the meeting included examining all available data related to a natural history of the disease, the disease pathogenesis, newborns screening method introduced in Ohio, and the current data on therapy. I

want to start out the discussion with the review of the disease pathogenesis. This is a graphic representation of the dystrophin lack of protein complex in closely allied proteins. Dystrophin that links the actin with the extracellular matrix to the [inaudible]. And stains of this of the muscle fiber and DMD, the absence of dystrophin is evident in the far right panel. This slide displays the consequences of absent dystrophin. Here we see a muscle fiber with membrane tears that get bigger over time and increase in number. The process continues with scar formation -- scar formation and fiber loss, and the result is a characteristic picture of dystrophic muscle. Here we see representative muscle biopsies of DMD boys. At the top left pad, connective tissue already replaced muscle fibers as early as three years of age. And more profound muscle loss over time. Observe the nine-year-old Duchene patient. When we discussed the natural history of the disease, we considered what we call the pre-steroid era, which is shown on this slide. Onset on the disease manifests as soon as 15 months with delayed walking. By age two-and-a-half, boys can no longer keep up with peers, and motor skills like walking and running. By age 3½, falls are more frequent and stair climbing is difficult. The mean age of diagnosis is around age 5. Patients are wheelchair dependent, usually by 9½ to 10 years old and scoliosis is apparent by age 12. By late teenage years, patients have more frequent chest infections and often have a dilated cardiomyopathy. Death can ensue any time after the late teens and early 20s. Recently, the natural history of DMD was better defined in infancy. This was done in MDA clinical network that involved the medical centers at Boston Children's; Nationwide Children's in Columbus, Ohio; St. Louis Children's; University of Minnesota; and UC Davis. Twenty four DMD boys with proven mutations, ages three months to about three years of age, participated in the trial, or in the study, really. Using the Bayley three motor assessment scales of infants and young boys with Duchene Muscular Dystrophy, we see that compared to normal, the gross motor score, the fine motor score and composite motor score are all abnormal in this very young population. This slide shows a shift to the left, representative of impaired development of young children with Duchene Dystrophy, with compared to normal using a composite motor score. Next we see what I would consider a very important graph, showing motor loss can be seen and measured and Duchene Dystrophy over the first three years of life. This creates opportunity for treatment with these very young patients. I now like to switch topics to talk about newborn screening and the introduction of the two-tier screening approach in the state of Ohio. Newborn screening for Duchene Dystrophy goes back to 1979, and has been done in multiple countries throughout the world. One of the most remarkable things is a consistency between programs and overall incidence of about one in about 5,000 newborn males. The worldwide prototypical approach has been to use a single tier system. Obtaining Creatine Kinase (CK) on dried blood spots of birth, or shortly thereafter, if it is elevated, CK is retested on a venous blood sample at the six week checkup. If persistently elevated, then DNA is obtained for DMD mutation analysis. In Ohio and in most places in the USA, the single tiered system would meet resistance because it is difficult to track every newborn after they are discharged from the hospital. In 2004, the CDC funded Nationwide Children's Hospital to establish a two-tiered system of testing. According to this paradigm, both CK and DNA are done on the same sample. This would fit the current practice of early hospital discharge within 24 to 48 hours post-birth. The source of testing is the dried blood spot card. In Ohio, dried blood spot cards contain five samples. Two go to mandatory newborn screening tests. This leaves three blood spots that can be used for CK and DNA testing. Our approach for newborn screening was established in several phases. The first and very important phase was the necessary testing to determine a population-based range of CK. This was done in collaboration with the Ohio Department of Health, where over 30,000 anonymous samples were used to establish the normal range of CK. As it turns out, that mean CK at birth was 247. And 593,

a number close to 600, was three standard deviations from the mean. We therefore chose to use 600 as a threshold for DNA testing. We also looked at CK in relation to gender, collection time, and infant weight. We detected no relation to difference in gender, collection time, and infant weight. The CKs could be done within five days. -- without any loss of CK determination, and the weight also had very little of fact, down to 1500 g. And the next thing that was important before starting a newborn screening program was to validate DNA testing on dried blood spots. This was done in collaboration with Bob Weiss at the University of Utah Genome Center. Extracted DNA was initially screened using a method called SCAIP that screens all Exons from mutations. If no DNA mutation was found in scape, the testing was expanded to include Multiplex ligation dependent-probe amplification, or MLPA, to identify deletions and duplications. In selected cases this was followed by DNA sequencing. Validation of these methods was done through a blinded analysis in the MDA clinic at Nationwide Children's Hospital and consented patients. This involved taking venous blood from patients and putting it on a dried blood spot card, and sending it to the Utah lab. These were known mutations, and this process all patients were identified correctly. At this point, we are ready to move toward our first study of newborn screening for DMD. Both the range of normal CK had been established, and there was complete confidence that any DMD mutation could be identified on the dried blood spot card. In the first round of newborn screening, 6,928 newborns were screened in four birthing hospitals in Columbus, Ohio and Cincinnati, Ohio. 110 exceeded the threshold of 600, and 2 of these were found to be above 2000. Only the two above 2000 turned out to have DMD mutations. In this first round of screening, we had 108 false positives of the 6,000 false positives of the 6,928 samples, or 6,926 samples, as a number that equals -- incidence of 1.6%. It also became clear that CKs that were high but not above 2,000 and did not have a DMD mutation would return to normal at the six week checkup. Thus, false positives could be excluded by either DNA testing for DMD mutations, or a recheck at six weeks for a persistently elevated CK. To increase our numbers, we extended newborn screening to 43 birthing hospitals in the state of Ohio. We raise the threshold for DNA testing to a CK of 750, now that we had identified only those above 2,000 as having DMD. This reduced the need for screening by 68% -- a huge cost-saving. In this statewide study, we found another infant with a CK above 2,000 and he had Duchene Muscular Dystrophy. We then added another cohort through anonymous screening of dried blood spots throughout the state of Ohio. This increased our sample size by 19,884, bringing the total screen to 37,749 newborn males. Three additional DMD mutations were found in this cohort, in this larger cohort, and all the CKs were again above 2,000. This table shows the six patients that we identified with DMD. All were CKs above 2,000, and mutations were spread over the usual hotspots for DMD gene mutations. We added an additional extension study, and the final cohort we screened 18,763 females. A CK over 2,000 was found in two females. In this extension study, we also had seven males without DMD mutation. For these nine cases, two females and seven males, we extended gene analysis to include the most common forms of other muscular dystrophy, particularly limb girdle dystrophy, and we screen for does DYSF, SGCB, and FKRP mutations. This table shows that when CK is over 2,000 and DMD is not present, we can also identify mutation in other muscular dystrophy genes. Important outcomes for our newborns screening study in Ohio were the following. We validated a two-tiered system for newborn screening that is well-suited to OB practice in the USA, with mother and child discharged within 24 to 48 hours. Costs are also very reasonable, with CKs only costing a dollar per sample, and then if DNA is required, there is $150 sampling chart. All DMD mutations were associated with CK over 2,000. Comparative costs for making a diagnosis of DMD and a toddler or a five-year-old would be about $2,500-$3,000, including the cost first to see specials, and having a muscle biopsy,

and then performing DNA testing. The value added for two-tier analysis is that mutations in other muscular dystrophy genes can be identified. Now I'd like to review potential treatments and where we are in the treatment of this disease. First talking about glucocorticoids, and then followed by discussions of one of the most promising new forms of treatment called Exon skipping. Let's first look at Glucorticoid treatment. Although it had been suggested that prednisone could have an effect in DMD, it was not until 1989 that the efficacy was unequivocally proven in a double-blind randomized controlled trial of over 100 boys. This graph shows the muscle strength improved for three months and then leveled off and stabilized for the full duration of the six-month trial. In the same trial, functional improvement was established by time test for stair climbing, walking 9 m, standing from a supine position on the floor, and also patients increased breathing capacity. All these three sites were highly significant. Validation of these results were shown shortly after these studies, by demonstrating that the effect of prednisone, was those related with the loss of strength by about 50% when the dose of prednisone was reduced by 50%. Further efficacy is illustrated by long-term studies. Of particular importance, scoliosis one of the major disease-related complications, is reduced from a 90% incidence to approximately 30% for DMD boys taking prednisone for a mean of eight years. On the other end of the spectrum, the question of the earliest effect of steroids has also been addressed, and a 14 year follow-up study, treatment of DMD boys starting as early as 2.4 years, permitted ambulation beyond age 16, compared to untreated boys who lost their ability to walk by age 10 or younger. For some of the patients who were a little older, ambulation extended beyond that, even to 18. One further study of interest is a dosing regimen, comparing daily steroids to weekend dosing, demonstrating preservation of linear growth by the weekend regimen. This reduces the incidence of short stature, a known steroid side effect related to long-term treatment. I also want to discuss one most promising method of treatment that is recently been recognized, called exon skipping. And a one-year double-blind randomized controlled trial of Exon skipping; we showed significant improvement in walking ability. This slide demonstrates a mutation of the DMD gene, in the upper frame, with the deletions of Exon 49 and 50. If we treat this patient with Eteplirsen and skip Exon 51, it will put the gene back in frame and allow for production of significant dystrophin. Etepliren is an RNA modulator that permits Exon skipping at a pre-mRNA level, it belongs to the chemical group called Morpholino. For this trial, patients receive weekly doses by IV infusion. The study design is shown on this slide. Three cohorts were treated, low dose at 30 mg per kilogram; hi dose at 50 mg per kilogram and a placebo group. Muscle biopsies were done at different times, to determine the dose or the duration of treatment was more important in establishing efficacy. After the first six months, the placebo patients rolled over to treatment with Etepliren and the study continued for the duration. Outcomes for this trial included dystrophin production; distance walked on the 6 m walk test and of course a series of safety measures. This is a somewhat complicated slide, but this shows that at 12 weeks, the high-dose patients represented by the gray bars were not making dystrophin. But at the six-month time point, all patients were producing dystrophin, indicating that the duration of treatment was a more significant effect than dose. Over on the far right, the placebo patients that rolled over to treatment also produced dystrophin after six months of treatment. Here, representative examples of increasing dystrophin production going from pretreatment to six months to one year. These are for patients with three biopsies, and you can see, increased dystrophin level at these different time points. This -- the most important question in any clinical trial -- is whether or not function improves. Here we see the upper purple line, that after 48 weeks of treatment, there is improvement in distance walked on the 6 m walk -- on a 6 min. walk test. Comparing this to placebo group the bottom yellow line, we see a decline in function for 36 weeks, but then a slow trend toward improvement once placebo

patients are on treatment. The pattern of improvement can be correlated with dystrophin levels. The continuously treated patients in the purple line started producing dystrophin between 12 and 24 weeks after an initial delay, and the placebo patients continue to decline -- until they started to produce dystrophin at about week 36. One of the most amazing things and gratifying aspects of this study is that boys participating in this trial came from hundreds of miles away for IV treatments every week and never missed a dose, and never had a single dose-related side effect, so what you see here are what we expect to see as a normal range of illnesses related to a pediatric age group. On the final slide, I have summarized the current status of newborn screening and Duchene Dystrophy. First, we do have a valid screening test that is highly sensitive, with a low false positive rate and unequivocal predictive value. Treatment outcomes for over 20 years indicate that glucocorticoids are effective and if started at a young age, can prolong ambulation beyond age 16. We can also prevent scoliosis, one of the most debilitating complications of the disease. We have a well-defined natural history of disease from infancy to mid and later childhood. And finally, the cost-benefit ratio that -- where a diagnosis in the newborn period reduces the cost by 10 to 20 fold, compared to diagnosis in mid and later childhood. And the other aspect of that, it can I avoid the diagnostic Odyssey, so that's the status current status of newborn reading that we reviewed at the MDA at the MDA symposium in September, and I want to thank you for -- for your attention to this, and listening to where we are currently at the present time and I'd like to throw it open for questions, thank you.

Thank you Dr. Mendell. Just a remind everyone that the condition is not been brought forward to the Secretary's committee at the moment and the decision to bringing this information to us was made based on the fact that this symposium was put together under the hubris of another Advisory Committee so gave us -- [indiscernible - low volume] [Indiscernible - poor audio] let's open this to questions, first from the committee and then from the -- let's have all the lines open

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All lines are currently open and interactive.

Thank you very much. Questions from the committee?

This is Jeff Botkin. I have three relatively quick questions. My understanding would be then that the CK, followed by DNA analysis, would not identify carrier females with the protocol. I'll go ahead with the three questions -- and you can answer. Secondly, it sounds like the definitive diagnosis was made again the CK and DNA analysis, and there was no muscle biopsy done to confirm diagnosis in the affected kids. And then my third question is, what parental permission model did you use for the clinical screening part of the studies?

Let me start the easiest question first. The parental permission model was -- was a consent model. This study was funded by the CDC and from the very beginning they mandated that we do, that we can send all patients for this trial, it became quite arduous as you see with the sample size and when we spread from Columbus and Cincinnati to a statewide. It was a challenge but we feel good that we got it done. Now CK, and let's just say that you asked about CK and DNA, and that no muscle biopsy or another way of saying it is that, is that sufficient confirmation and that's absolutely correct, that DNA analysis is the gold standard for this disease, and we've moved up in the last decade from being able to identify only about 65% of mutations now with MLPA and sequencing to identify over 95% of the DMD boys would Duchenne Dystrophy and we have very good

database between here and children -- between here and University of Utah, we have over 1,500 patients that have been look that with a good perspective on the DNA mutations. We also have the Leiden database, which is a well-known database for Duchenne Dystrophy. Now the carrier question is more challenging. We have no reason to suspect that we couldn't identify carriers. We know that carriers are – that CK carriers are increased especially early in their life and over time CKs drop-down, because there is preferential selection and of nuclei that are expressing dystrophin and with the loss of the nuclei that don't express dystrophin, even if we put this at 50-50, we would have a gradual replacement of most of the muscle fibers now expressing dystrophin in the CK dropping down. So we think that we could identify carriers, if that became important, and we could do this once having the CK elevation, we could do DNA testing. Remember that we left a window (and we didn't have to see it amongst these nearly 40,000 patients who may be not unusual, but the CK would be -- we started out at 600. We ratcheted it up to 75o to cut down on cost because the CKs were turning out to be over 2000. We had plenty of room between 750 and 2000 to identify carriers, and we suspect that we would -- as to how we would handle those, is that got considerable discussion at the symposium. And how -- we would try to use a model that had been -- that's used for other diseases that have been applied for carrier detections. It's my understanding, and I'm sure your committee knows this better than I do, but in diseases like CF and some of the other diseases, carriers are not detected, and it's determined on a state by state basis and we have plenty of time and identify Duchene patients to identify carriers. But if there was a strong movement toward identifying carriers, I'm quite sure that we could accomplish that.

Thank you. Additional questions? Any members?

This is Dieter. I just wonder about the treatment, the Exon skipping treatment, is that currently available or is it only under study protocol?

Currently, it's only under study protocols, but there is a strong move to take this to the FDA. And that will be an FDA decision as to whether it will be fast tracked or not. We will wait and see. There are compelling reasons, we have support from multiple families who have been participating in these trials. For example, there is one foundation with over 150,000 signatures, and they are going to the FDA to appeal to the FDA for approval of Exon skipping. And like I said, it is a very promising form of treatment and of course I'm hoping for approval, because that would extend the ability to treat many more boys then we were able to under protocol.

Additional questions?

Dieter again, are you planning to bring this to the Advisory Committee for request for consideration for newborn screening?

I certainly would appreciate the opportunity. I think there was a little bit of confusion about how this got on the agenda today. But there was -- it was my intention actually to do that, and I think it was not -- the nomination was not in the traditional sense of the SACHDNC, but I felt I wanted to move ahead with this presentation in any case because one of the things that we found at the MDA symposium on newborn screening was that most of the people outside the field -- outside the expertise of the clinical disease -- were quite amazed about how far things had advance. In general, many of the newborn screeners who were very contributory stood up at the end of the meeting and

said they were very grateful to see -- how much progress had been made in this area. That was certainly an impetus to present here today, and to open it up for discussion. But I would like to come back and present it as a formal nomination.

Yes, unfortunately we don't have that as an alternative. There's a formal scheduled way to do it

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I understand that.

We would love to see your nomination package come through.

That is enough of an impetus to do it. Thank you very much.

Additional questions?

Dieter again, another question, suggestion, you may want to contact in NBSTRN and we are now to see if you couldn't your data into a new portal for Duchene Muscular Dystrophy given all the data you have already. I think that would be a good starting point.

Thank you.

Additional questions or comments -- anything from the liaisons or Organizational Representatives?

This is Cate Walsh Vockley. I was just wondering if there's any evidence from clinical follow-up for patients with false negatives, and whether or not any patients were ultimately identified as having mutations were consistent with macro muscular dystrophy identified?

Well but honestly, the distinction between Duchene and Becker dystrophy in infancy is mostly as to whether a gene is in frame or out of frame in terms of its mutation. There are many and accuracies to that as to whether they are truly Becker or truly Duchenne. We have many examples of in frame mutations that turn out to be Duchene. That is a, I think, -- if we have screening, it would be unclear as to -- for the in frame mutations as to whether they have Becker or to Duchenne. As well as false-negative goes, one of the things I was occurs about in the study was that if they for the CKs that were less than 2,000 we consistently as part of the study, we made an attempt to follow every patient and contact their PCP and ask if they get the CK at their initial checkup and what we found was that -- showed the CKs were less than 2,000 we have CKs that were returned to normal. As far as CKs over 2,000, that was one point I was trying to drive home was that we can identify other muscular dystrophy mutations – not in Duchenne mutations, if the Duchene mutations were negative we were able to -- this was really a proof of principle more than anything else -- I've been asked this numerous times and this came up at the newborn screening symposium as well, how would we handle that? Well our approach that we actually had as part of our protocol is, if the CK was over 2,000, we would contact the PCP and discuss it with them and asked that the patients be followed in any one of the 200 MDA clinics that were around the country -- the ones that would be closest and most accessible to the patient, so that we had that built into the protocol. I think that's how we would recommend doing it. We wouldn’t want to recommend that every non-Duchene patient likely as a form of muscular dystrophy then go onto -- through this -- to this method and have an analysis for identifying other genes. We'd rather do that in a clinical

setting, and we have very good opportunities to do that. Our clinics are very receptive to seeing these young infants and trying to make a diagnosis in those very young infants. We had that in part of the protocol and I think in a newborn screening program, that's how we would move forward to over -- over 2,000 in those very young infants. We had that in part of the protocol and I think and a newborn screening program, that's how we would move forward to over -- over 2,000 DMD they we would discuss that with the PCP and ask for follow-up of those patients or at least inform them. They would obviously have a choice as to whether they wanted to where they could reserve it for a later time.

All right, additional questions or comments? If not, thank you Dr. Mendell. We look forward to hearing from you again.

Thank you.

That will conclude this part of the morning session and we now have a 15 min. break. That's 10 min. early why don't we return at 35 min. after the hour and start the subcommittee reports 10 min. early. All right, enjoy your break, we will see you back in 35 min. after the hour.

[The event is on a 35 min. break]

[Captioners Transitioning]

Is everybody on board? We are ready to start the next phase of the meeting, and that is the subcommittee reports. The first report is a laboratory standards and procedures, and Carla will do the presentation because Dr. Lorey is unable to attend. We could open Carla a phone line to meet everyone else. -- Mute everyone else.

Okay, can you hear me? Thank you again for allowing me to do this. I hope Fred Lorey is listening in, but I kind of doubt that. I want to talk to you about some of the presentations that we had our meeting yesterday. First of all, we welcome some of our new members, it is actually nice to see the level of interest from these individuals and we look forward to their participation.

One of the presentations that we had is updated by Jelili Ojodu. He has been doing a lot of presentations recently. He gave us some updates on some of the activity on the newborn screening and genetic public-health program, which is a program he oversees. We have talked about the 50 years of newborn screening presentation that will be underway in 2013. So he gave us an update about the different exhibits that will be featured in 13 different states and health departments, so that is going to present some level of excitement within those areas, especially as they get a greater understanding of the benefits of newborn screening. -- Is also going to be leading on some of the exhibits of different professional meetings and the newborn screening meaning in Atlanta, AAP, APHA, etc. Work is well underway and they're expecting a publication of the coffee table book, and hopefully an e-book that would be associated with that as well. We talked about some social media outreach, media coverage for this activity and give us a reminder of a Washington DC reception and awards ceremony that will be happening in September, mostly targeted toward elected officials and leadership, to bring awareness to them of the benefits of newborn screening.

Jelili also talked about the newborns screening and genetic testing symposium. That will be held at the same time as the International Society for Prenatal Screening that is going to be in Atlanta May 5th through 10th, cosponsored by APHL and CDC. This year's theme is 50 years of newborn screening, celebrating the past and preparing for the future. In addition to a very hefty program that they have for five days, they also have laboratory tours CDC, that is the newborn screening and molecular biology bridge, at the Georgia public-health laboratory. Registration is currently open and available on the website. APHL has been very much involved in a program with the CDC, and that is called the molecular assessment program. This program was developed to address specific concerns as states implement molecular testing into their routine workflow. This came as a result of it as SCID but we are anticipating other molecular testing and some laboratory are doing molecular testing in different forms. We want to make sure resources are available to all of the states as they start moving in this direction. The goal is to provide feedback to CDC report to the newborn screening laboratory on their molecular testing capabilities to suggest improvements through a peer review process. This is a friendly site visit, it is absolutely not regulatory, and CDC is not a regulatory agency. The representatives of this include members from CDC from various states and laboratories and APHL. During the pilot phase, visits were made to New York, Wisconsin, and Washington state, and we have recently had visits to Texas and Florida, and Minnesota is anticipating a visit from this particular team in February. Requests for the lab visits can be made through the website.

I was given an update about the newborn screening assistance and technical program, which we know as a typo there, reminded us about the admission program overview and goals, and described many of the accomplishments so far. Building the teams, networking, creating a national presence, talking about the committee and the steering committee guided activities. The fact that they're going to be incorporating various quality indicators in case definitions, and all of these things are going to be aimed a continuous quality improvement for screening program. So that was exciting to hear about again.

Swapna Abhyankar also presented to us and she talked about newborn screening Health IT initiatives, and give us an update of their work at the National Library of Medicine. This was actually focused more on Critical Congenital Heart Disease, and she give us an update on where they were with the creation of LOINC terms for CCHD. Terms have been created based on input from CMNC, HRSA CCHD technical assistance committee and grantees and from Oz systems. The LOINC terms again were lined with implementation guides, and they currently cover only the screening results and these have been submitted to registries and they are waiting for the codes. Work is ongoing and there are a number of CCHD terms currently being requested, so they have a lot of work ahead of them. She also mentioned to us that they had -- they were also working on mutation nomenclature so they have are aligned with the HL7 Implementation Guide, created a LOINC list for cystic fibrosis mutation results, and again they are working with the Regenstrief Institute to figure out the best way to incorporate mutation synonyms and related information into the answer list. One of the things she needs information from the states about is which conditions include mutation testing as part of newborn screening, which states are sort of independent and using mutation testing and reporting out as part of their reporting package. And what specific mutations are being screened for and how reports are being reported. She reminded us of her e-mail address, and everyone who is interested in getting back to her about that, she would like more information that she works on this part of the project as well.

One of the other talks was by Dr. Matern of the Mayo Clinic, and this particular presentation addressed one of the priorities of the subcommittee, and really was looking at evaluating some of the markers that we currently use for testing and newborn screening. We were looking at newer screening for Tyrosinemia Type I, the markers that has originally been associated with testing the Tyrosine itself. So the question arose, could we move to Succinylacetone, and the answer would be yes. So Dieter gave a very extensive and wonderful presentation, and I am not going to summarize that**.** It would be best if he did that as a formal presentation. We are hoping to present this to the committee itself. This will be whenever the next committee meeting will be, once we have finished our data collection. Pretty much, he gave his an overview of Tyrosine Type I and it has incidence of one and 100,000 live births. There are higher incidences in Québec which is one of 17,000. Failure and death in infancy are chronic forms, which also resulted in hepato-renal symptoms. The biggest concern for this condition is that Tyrosine is really not a specific marker for Tyrosinemia Type I. Tyrosimemia is also elevated in Tyrosinemia Type II, Tyrosinemia Type III, Tyrosinemia of the newborn, and it is also elevated in liver disease. Succinylactone, on the other hand, is a very specific marker for Tyrosinemia type I, but in the original essays that were developed for newborn screening, was not present as a marker. You may consider possible screening options, or you can remove it. The states could choose to do that. You can lower the cut off for Tyrosinemia, and except the poor sensitivity implemented with it, we can implement the alternative marker using succinylacetone as a primary marker or a secondary marker when Tyrosine is above a clinically significant cut off.

The data presented a lot of wonderful slides, which I won't represent everything, just another two or three slides here. But this is data that comes from the Region for Genetics Collaborative, and many of you might be familiar with, but just to show you on this axis here, you can see the different types of diseases and I apologize if you cannot see them. On the Y axis is the concentration of Tyrosine, but the green area represents the normal range or different types of cutoff that you would expect with the different states, so you can see there is a very wide range of cutoff. The fourth bar here represents the range of Tyrosine levels for patients with Tyrosinemia type I. You can see there is a significant overlap between the green area that represents the normal range and the concentrations of Tyrosine associated with Tyrosinemia type I. This really points to the fact that Tyrosine is really not the best marker to distinguish between a normal and effective population. Succinylactone, on the other hand, has been shown to be much better and this is a -- from Mayo Clinic. Here is where on the x-axis they show the concentration of Succinylacetone and the spread of the normal values, and you can see that it is very distinctly separated out from the Tyrosinemia Type I cases.

This slide is a slide that we put together from available information that describes the kinds of testing platforms that the different states are using, so in the light blue you see the states are using Tyrosine is a primary marker, Succinylacetone as primary marker is shown in yellow, orange states that use Tyrosine as a primary marker and Succinylactone is a secondary marker, and the ones in dark blue have been reported to not screen for Tyrosinemia type I.

In addition to putting this together, this is a project through the committee and Dieter Matern of the Mayo Clinic and some of us at the CDC are gathering data and putting together information to address with some of the issues actually are. Kinds of reports we really hope to submit would

include information that would describe some of the limitations and challenges that they might have in regards to Succinylacetone implementation. Sometime in October, some of our group at the CDC interviewed a number of different states and interviewed states that were measuring Succinylacetone and others were not, and got a sense of how -- what some of the challenges were. That is something that we certainly will be reporting on at our next meeting. But at the same time, we also put together a survey package and got the Office of Management and Budget to give us permission to survey all of the states to get a better sense of where all of the states actually were. These questions are present in the next couple -- next two slides so for the laboratories measuring Succinylacetone, we pretty much asked them, do they measure Succinylacetone only in response to elevated levels of Tyrosine? Do they use it as a secondary test, or do they use both of these values and capture and report both of them? Analyze budget restrictions, were they an issue? Were any of these considered obstacles? And if so, how do they overcome them? For the laboratories that were not measuring Succinylacetone, we asked whether they are even considering the adoption of Succinylacetone testing. We were going to be asking about whether or not they are planning to do so in the future, or asking for necessary funding infrastructure or technical expertise, but their obstacles has -- have been or are, and this question was really for us, whether or not the effect of a formal recommendation by the committee itself or the Secretary, or the SACHDNC itself would be helpful to move that process along, or would it not? And finally an open-ended question, about what the largest challenge to implementation would actually be? So those are the responses from those surveys, together with some of the background information, that we put together are all going to be put together into a report and we will be presenting that to the SACHDNC, hopefully at the next meeting..

Will the report that you generate be placed in the MMWR as well? Is that the goal?

We can certainly do that. Perhaps what we would do is presented to the SACHDNC, and get some of your feedback so that we can actually prepare that as some kind of report and recommendation.

Thank you for it – nice summary of your activities and report.

Additional questions for Carla?

All lines are currently open.

Everyone is so quiet today. I don't think you will jump in on top of each other.

This is Ed McCabe. Just with the states that are not screening for Tyrosinemia, have they given any indication of why they are not screening?

We have yet to put together that information, and I think we will have a more comprehensive understanding at our next meeting. We only got the approval from OMB on Wednesday, so we do have all of these questions ready to go, but we still have to put that out.

We are going to combine that with information we have gotten from the oral questions.

Thank you.

This is Carol. Clearly this will be a conversation for the whole community, but you asked an interesting question that I would just like to highlight. I think what I would like to know is if this is true, that if this committee were to make a recommendation for a specific metabolite or specific method of testing, that would be breaking new ground for the committee? Because I think the committee has suggested conditions and not specific tests.

Thank you, and yes that did come up. We understood that when we put that as part of the survey, that it was a provocative question. So we are not saying that is the next step, but we are asking what the sense of the states are, whether it is something that they would -- we just want to get a sense from the states. I am sure when they have a chance to respond in their questions, they will let us know what they think.

That would be combined with information and the point of view from the committee itself.

This is Carol, I just want to highlight exactly what you said that will be interesting to see what the states say but would be a novel thing for the committee.

We completely understand that.

This is Ed McCabe, from the March of Dimes. Just to remind everyone, the document put out by the door -- by the joint HRSA committee background 2000-2001 recommended standardization not only of testing across the nation, but also technologies.

Thank you, Ed.

This is Susan Tanksley, representing APHL. I know you showed the questions and I cannot remember if this was on there, but the mention of incidents, historically or what we think the incidents to be, is about one and 100,000 and you showed much higher incidence in Québec. And I think I recall him saying that it was about one in 700,000 in Minnesota, and since we have been screening with Succinylacetone in Texas since early 2010, we have only identified one case of Tyrosinemia Type I. That puts it somewhere at the much lower incidence as Dieter mentioned. I was wondering if there is a possibility of asking that as well.

We will see if we can incorporate that. That is a good idea because again it seems to be very rare.

This is Carol again. Unless I misunderstood something in the discussion of the sensitivity, I would just be cautious about concluding that the number of babies found by newborn screening is equal to the incidence of the disease, because I think it is my understanding that we expect to miss some because the Tyrosine is not always elevated.

Correct, correct. Thank you, Carol

This is Susan again, I would agree with that if you are screening with Tyrosine as the marker, we know that we missed two cases of Tyrosinemia Type I while we were screening with Tyrosine. We have only identified one case since we switched to Succinylacetone. So it would be interesting to

see what has been identified using Succinylacetone as the marker, as well as using Tyrosinemia. Whatever is known by the state.

Those would be good questions to add and include.

Any additional questions? If not, thank you and we appreciate your presentation.

This is Chris, can I say something? I just want to follow-up with Carol's comment about the committee recommended conditions, and how does this play out? In recommending a condition, the analysis is based on a specific test, and the data from that. So how do you bring those things together in some sense? We only recommend a condition because we think that there is data out there, that there's a test that meets certain criteria that allows us to move on.

I think that is the crux of the question. My understanding is that the committee has never recommended any specific tests, so the important question here is whether we can add information that will clarify some issues and then whether it would be better to have data as it comes out with the additional -- that have already been spoken about. To inform states about false negatives and the relative value of one procedure to the other rather than having recommendations specifically coming from the committee.

The data will speak for itself, and it would be on the strength of the data that I would think people would want to move one way or the other.

It looked like a large number of states are already using Succinylacetone.

Correct, so it would be interesting to see why some states have not chosen to move in that direction.

This is Dieter can I make a comment? In my presentation yesterday, it looks that maybe there is only one test to screen for Succinylacetone, but I think they're really talking about adding it as a marker for Tyrosinemia Type I. How that is done, I don't think we have to care about the multiple ways of doing it. So I don't think we will have to suggest a particular assay. That can be left to the programs. But I think Succinylacetone is clearly superior for screening than Tyrosinemia Type I.

Thank you. Additional questions or comments? If not, thank you, Carla.

Don has the presentation for the Subcommittee on Education and Training, I think your line is open so you should be able to speak to us.

Can everyone hear me?

Okay, great. We had a great meeting yesterday so I will give a summary of what we tried to accomplish. Just to remind everybody, I like to do this at every meeting, we have a very broad -- we're supposed to review existing training resources, and identify gaps in education and training nationally and make recommendations regarding five groups. The parents, the public, and a variety of different health professionals. To help us do that, we have a broad representation on our

subcommittee. We have five members of the Advisory Committee, and a number of organizational representatives. Mary Willis was able to join us from the Department of Defense yesterday, and I don't know what the status in the future of our Department of Defense representatives, but we look forward to continuing that. Lisa Bunjo is now a new member of our committee. We have one Federal funded grantee from the regional collaboratives, as well as facilities, parents, and state labs.

We had goals for our meeting. The first one was to finalize the process by which we reviewed conditions for possible screening outside the newborn period, then to discuss the status of recommendations for picking a prototype condition to guide our work going forward. As with Carla's committee, we didn't want to hear updates on the CDC and APHL newborn screening awareness activities, to begin to provide feedback on one of those products which is a draft of newborn screening brochure. Carla present much of that information already so I can short part of the presentation related to this. And surely, one of our activities is to prepare plain language summaries of -- either nominated or reviewed and not approved, and I will give you some background information on why we are doing that and where we are with.

The first project under priority A is to identify one condition that is not a part of the RUSP, for which screening and treatment most likely would occur at a later point in child development. But once you identify that condition, work with professional organizations, researchers, clinicians, and identify major needs for that condition. Why are we doing that? If you go back to the Charter for our committee, in the very first few sentences it says that the overall committee is in charge of advising for childhood screening . Just about all of our work has been focused on newborn screening and appropriately so. But in the larger committee, we felt that exploratory work is needed, to start to understand what would be the challenges and opportunities inherent future attempts to make national recommendations regarding childhood screening. Whatever something was brought forward in the childhood screening arena? Who we make a recommendation to, and who is the infrastructure for implementing childhood screening in the way it is for newborn screening? We want to take a condition, so we have the subcommittee agreed to begin this exploration.

Our approach, and we wrote a one-page summary of how we are going about this, for the reasons I will just show here. The way we're going about this is to take up a best case example or an exemplary condition approaches our strategy, and we will pick a good example and use it to explore the issues and challenges and opportunities that will arise if the committee were to consider priorities for screening for conditions after the newborn period. We want to make clear because several people have questions about this, about what is not the purpose. We are not planning to create a policy recommendation for the exemplar condition. If we were to do that, it would set up a whole another dynamic and change the way we pick the condition. Rather, we are trying to use it as a case study to determine whether or not we should approach training needs in the future. So the timeline so far is in the summer of 2012, we asked for nominations for conditions for different subcommittee members and other organizations. We got a good substantial list. We narrowed those down., took out some conditions where there was not a clear diagnostic tests for, and Beth led a discussion of this in the Secretary's Advisory Committee. You gave us some feedback and asked us to be a little more formal or structured in narrowing it down to pick it condition, so we created a rating scale and circled around the subcommittee members, and then yesterday had an extensive discussion where we review the conditions that were on the list. At the end of today, we cannot

narrow it down to one condition, we felt like it would be good for us to pick more than one because different conditions people different kinds of issues. So the three conditions that we selected our -- Fragile X syndrome, Long QT syndrome and Wilson's disease. I will give you a quick run through of these.

Our plan going forward has not been developed yet, but during the spring and fall of 2013 is to solicit input from a variety of stakeholders relative to these three conditions. This would include the major advocacy organizations, people who have done research in these conditions, and clinicians. We will be doing this both in the context of our formal committee meetings and hopefully some interim conference calls. We are intent -- our intent right now is to report back to the Secretary's Advisory Committee a year from now, in the winter 2014 meeting, about lessons learned and what would be the implications of what we have learned from this process for the committee, if we start considering conditions.

Let me briefly describe each of them. Fragile X syndrome is the most common inherited form of intellectual disability, is a single gene disorder and the rate is not known but probably one in 4000 to 1 in 5,000 males, maybe not quite as many females but that is still unknown. Average age of diagnosis for males who have what the full mutation is around 36 months of age. What happens is as I mentioned a little later, the children miss out on them opportunity to participate in early intervention programs, and we have shown that 25 to 30% of families have a second or third child with Fragile X syndrome before the first child is identified. There have been a number of tests that have been proposed, ad are being used in pilot studies right now. There a DNA-based test so the good and bad news is that the DNA-based test would also identify carriers. They're much more common than affected children, so in our latest data from a couple of studies, it looks about one in 200 females and one in 400 males are carriers. What is complicating this is that carriers are at risk for late onset disorders, and perhaps other cognitive and emotional problems. Currently, professional organizations recommended in a child with the development be referred for fragile X testing. This is not really happening in any consistent way. Research has led to a whole new generation of targeted treatment of very effective in animal models in clinical trials underway for adolescents and adults with several companies and some pediatric trials of getting started, but those are going down to five years or older.

So Fragile X syndrome is one good example of a condition that could benefit through some kind of systematic screening policy after the newborn period. One of the discussions we had in our committee is whether we are talking about population screening, or targeted screening based on some initial symptoms. If we took on this -- one approach would be population screening of all one year olds, for example, or would be more targeting screening for a child who shows developmental delays and to the pediatric [inaudible].

So we have not come down to population or targeted, but in these conditions we would actually be talking about targeted screening.

On Long QT syndrome, I am not a physician so take these descriptions with a bit of salt, but I did open back to our subcommittee, and so far it looks like we are pretty active here. Our syndrome is a disorder of heart and electrical activity related to malfunction, probably about one in 3,000, and they can cause the sudden uncontrollable dangerous arrhythmias in response to exercise or stress.

10 or more times of Long QT Syndrome (LQTS), many of them with gene associations, there are probably some others of unknown origin. Looks like half of people have untreated inherited forms of acute LQTS dialysis tech is so it is clearly a fatal condition but many people. There are treatments available which include lifestyle changes in dietary adjustments, a selected the medication avoidance etc.

The absence of any kind of family history, identification depends on clinical symptoms which would ultimately require an EKG and a gene test is about 75% more likely to identify the mutation to meet clinical criteria. Most identified patients have an effective parents, so identifying a child with this condition clearly would implicate a parent, but not all of them have been recognized until their child has had a cardiac event. Urgent treatment the first two months of life is probably not justified, but the early identification of conflict could be important for prevention. You can see the Long QT syndrome evokes a different set of issues that Fragile X syndrome and we think it would be an informative condition.

The third one is Wilson's disease. This is a recessive single gene disorder. Is well-characterized molecularly and more rare than other conditions we have mentioned so far, probably one and 30,000. In this condition, copper is not eliminated properly so it leads to a buildup in the body tissues and damages the liver and nervous system. There is a range of ages but usually by age 4 -- without treatment and can be fatal or severely disabling. Treatment usually involves lifelong treatment and possibly with additional dietary and exercise routines, the treatment could substantially alter outcomes. Symptom-based diagnosis is challenging relates to perform diagnostic odysseys. Wilson's disease can be differentiated -- difficult to differentiate from other liver diseases and symptoms they gradually evolve over time. We have considered 11 different conditions, and we want to say that the conditions we eliminated were not important conditions, but we thought these three would be great examples of conditions where a good bit is known already, and they are each posing different kinds of opportunities for us to learn about opportunities and challenges in later childhood screening.

Our second priority is focusing on newborn screening awareness, and our main work here is providing background and back up support and input on the 2013 newborn screening awareness campaign plans and activities. Once this year is over, our responsibility will be to identify ongoing strategies for newborn screening awareness after 2013. We are all excited about the 50 year anniversary, there will be a lot of activities going on, the newborn screening will continue after 2013 and we want to make sure that awareness is more institutionalized.

I popped in some slides that Carla went through, so I will just highlight a few things. The purpose of this broad-based campaign is that it is a national campaign to celebrate achievements and raise awareness and is cosponsored by the APHL and CDC, and a variety of other partners that have been very successful in getting funding from a variety of different sources.

Would we want to get information out to? Really, everybody. The audience included expectant parents, families, a variety of different clinical settings, scientists, and state and national media.

One of the things they have done was, with the core message from the campaign and say what is the do we want to convey to the variety of activities? There are four core messages. These live, it is

a fast way to protect her baby, follow-up is not critical, if you get a call that your baby has a condition that is critical. Take appropriate action immediately.

Carla went through these activities very well so I will not describe them again. One of the activities listed here is an educational brochure. Jelili gave us a draft and final copy of the brochure, this group has reviewed it is never people have some suggestions, I think we have a very short turnaround time over the next week to get feedback back to Jelili, so our group is hopping on that and will definitely give some feedback in the next few days.

Carla mentioned the days of the 2013 APHL meeting, and the awards reception in Washington DC in ceremony will be observed September 18th.

Our third activity is to collaborate with the Condition Review Group to develop public friendly summaries of previously conducted evidence reviews as well as evidence reviewing nominations a have not come forward. Why are we doing this? There are two reasons for this. One is to increase public transparency for what we do and the rationale for the decisions that are made, and secondly to support future nominators and preparing successful application packages. The main activities here are to create short plain language summaries of the evidence reviews. We hope this gives guidance or blueprints for future nominators and the main way we would be doing that is improving information on the committee's website, and eventually create possibly a lessons learned case study book for future nominators. We have made quite a bit of progress on this and the consulting group is working and has been contracted by Atlas to help us with this and let by the senior leadership is providing quite a bit of support this activity. We have reviewed drafts of their write up of two conditions, and gave lots of feedback, so we're continuing to work on this. Our ultimate goal would be able -- would create a 30 or so page document that would be written in plain language for a broad audience and would include graphics that the committee processed, visuals, provide an overview of the broader Secretary's advisory committee, who we are and what we do, provide details about the RUSP. But really to focus on explanations of the nominating committee conditions that were either determined by the committee not to be ready for formal evidence review or after the events review we said we are not ready to move to the RUSP. These descriptions are the intended tool to help stakeholders see how the committee makes its decisions, and many of the reasons why a condition does not move forward. Again, the public stakeholders are to improve their own condition nominations. This is not really designed to provide a path for the conditions that have already been nominated and not approved. That is a different activity that will be a helpful thing for a committee or for the Secretary's Advisory Committee to take on. This goal is to revise some high level, big picture examples of the most common reasons why conditions get stopped at one point or another in the review process, so that if someone else has a condition they want to bring forward, they can see the major challenges of reasons why things have been rejected, and do their own due diligence in preparing their condition so that it is ready for a successful review.

In the next two or three weeks, we are hoping to have a draft of this document and we will review this and give feedback, do another round of revisions, and it will go out to the Education and Training Subcommittee for a more detailed review and we will be including a review by the consumer task force and other stakeholders. Our goal is to provide a final document to the full committee in April or May or whenever we hope to meet again for your review, and I guess at that

point we will discuss whether this is something to forward to the Secretary or simply post on the website or whatever.

That is a summary of the activities for our committee. I think I have done, and I will open it up for questions.

Could we open all the lines, please?

All lines are open and interactive.

Any questions from committee members or organizational members?

This is Chris. And your discussion of your representative conditions for childhood screening, with regard to Fragile X -- did you discuss newborn screening?

We recognize that different screening would be quite possible for Fragile X but that is probably not ready for prime time or as close to being ready as some other conditions. But we thought it would still be usable condition to study childhood screening. We're not excluding any of these for possible newborn screening.

I just want to point out that if you have any questions or comments, you can type them into the checkbox.

Additional questions?

If not, thank you very much. [Indiscernible - low volume]

Next we have the Subcommittee on Follow-up and Treatment, if we could leave Carol Green's phone on, and close all of the others, I don't know if Chris is going to present. If so, open Chris's line as well.

We are all the other lines.

Has the other speaker announced himself?

Chris, are you the second speaker here for this report?

I'm here, can you hear me?

Okay, please proceed.

Thank you. I also want to start with a heartfelt thank you to the members of the subcommittee who we had a terrific meeting, and we had a few extra members of the public who were very helpful during the meeting. The meeting itself was the culmination of many meetings since the last full committee meeting, and a lot of work has been done in the interim. Very useful meeting yesterday and what you're going to hear about reflects not just the meeting, but lots of work.

We are going to go through in the order we had it in the agenda. We started with a couple of reports to the subcommittee on some relevant projects. First we heard from HRSA project that had worked on the underpinning of coming to consensus about collection of outcomes data for children with inborn errors of metabolism (IBEM) detected by newborn screening.

We have asked Sue to present -- you will see this is relevant to our projects. If anybody is interested, she put together some very useful slides, I do not propose to recapitulate, but she described several years of work coming to consensus, initially on some core data elements and working with some of the regional collaboratives and professional organizations, to develop specific outcome measures for 40 inborn errors of metabolism as a research project. I do not remember exactly how many centers are now involve, but a number of centers have contributed information on more than 1,000 children with, I believe it's more than 20 disorders, and they are at a point where they have enough information on some of the more common conditions that they are beginning to develop reports from this database, and they are accepting other clinical centers to be part of the project and there are some potential strategies for funding participation for the data collection and if any centers are interested, that information is available through Sue Berry and the that regional collaborative. The whole committee heard from Amy Brower about NBSTRN , and particularly wanted to learn about the longitudinal pediatric data resource which we heard about the whole committee this morning because again, that activity is relevant to one of the projects of the subcommittee.

Next, we want to discuss -- I know that our projects have formal names for the full committee, the priority A and C and -- sorry, I did not go back to see how those names link up with the committee's names for the project, but we are not going to report on our two active projects. One which we are calling the EDHI project, which is the subcommittee that was charged to explore what lessons we have learned from hearing screening that could be relevant to CCHD screening in particular and any other point of care screening going forward. And, actually we did not know we could have both of those on the phone, so I did not ask, but Chris, would you like to present the next couple of slides?

I can do that. This one just says that as part of the project, there were really two things that we discussed at this part of the meeting. One was a newborn hearing screening survey that Brad Therell had done which asked questions of the hearing screening programs and got responses from 50 to 51 of them. And the second one was that we have had meetings talking about lessons learned from the newborn hearing programs that may be applicable. And actually Brad's survey informed some of that.

This talks about the survey that Brad did, for questions were asked of the screening programs. One of the specific ones was the idea -- are people using the blood spot greeting card or the electronic birth registration process as places where the hearing screening program gets results? There were other questions that asked about barriers in terms of newborn screening and Brad put together the responses, and our subcommittee members have received the survey results for further analysis. Some states were getting newborn blood spots greeting card, but it was not all of them, and even most of them, and in using it, it was hard to determine whether by doing that their program was approved. So that is going to take the further analysis. Next slide.

That we had a pretty rich discussion about lessons learned from the hearing screening projects that are applicable. Although specifically we were talking about Clinical Congenital Heart Disease, it was clear that there are some inherent differences in clinical congenital heart disease that are critical part, hearing screening is the follow-up of more outpatient follow-up, while Clinical Congenital Heart Disease would be in hospital follow-up and lost to follow-up may not be as big of a problem. We talked about some general things that we are going to flesh out with a smaller group of people who are interested in writing a draft that would be on these lessons learned. Some of the things that we have outlined that it seems to be the better you're able to -- the thought is, it if you link with other screening efforts, there may be a more impetus, and I think this came out of newborn screening, that there may be more of an emphasis of programs being part of an overall state program. The other general thing is the idea of state health department in terms of integrating whatever that means in terms of the screening data systems, we had a discussion specifically for the electronic nature of newborn hearing screening and the possibility of linking that directly with the CCHD screening in terms of electronics so that will be more fleshed out. And the other part which can specifically from newborn hearing screening is that the appropriate -- we always talk about whatever that means, financial support, federal state, it will be needed to develop the screening system. There is concern that the possibility of less support financially for hearing screening may affect the outcomes for that. So the end result of this is that, and we got quite a few volunteers to be in a small working group, and the hope would be the next meeting we will be able to present that to the full committee.

That is it for me.

So the next ongoing project is one that the full committee may recall having heard. It's called the sickle cell project, but to make it clear what we are and are not doing very much in the way that we just heard from Don, we do not want to have any misunderstandings that we would be proposing to do anything that would belong to a different group of experts or to go beyond our scope. For shorthand, the outcomes after newborn and the formal working title Write Now is a framework for assessing outcomes from newborn screening.

To remind the committee and everyone else, the charge from the committee stems from a question that was asked broadly, related to a presentation in that Alexis had done, and the question is, are we realizing the benefits that we anticipated when we started newborn screening for condition X? In order to understand whether we are achieving the expected or hoped for benefit, we need to know what the outcomes are.

What the committee has been doing for the past month is a combination of developing an early draft, and I will show you that draft in just a moment. This is an early draft of some of the key questions, which are very close to what the data needs. We were also asked to consider what are the data sources? And the resources currently available to answer these important questions, and one of the gaps in these data sources? Without actually collecting any data, our goals are to develop; I do not want this as a course site, but a framework of what are the key types of questions? Related that framework directly to the prior work of the committee that was very well summarized in a recent paper with Cindy Hinton -- is the first author, relating our outcome data needs to that basic framework and then developing some more detail so that it can be implemented with a focus on

developing a set of core data elements or types of elements that would be needed for any condition, and using sickle cell as an example, to make sure we are developing something practical, explore the framework in an iterative process, and explore the data available. Here's the current draft of a framework, and I have to give some thanks to Alexis Thompson, Cathy Hassell, Nancy Green, Cindy Hinton, and a few other people, forgive me if I have forgotten any names. It's a little small but hopefully people can see that we are trying to keep it rather simple.

Just basic questions about detection and looking for direct outcomes of appropriate interventions. We have to ask ourselves what is appropriate intervention? A first pass of populating one row, to give you an idea. Our initial draft is fairly well populated with an example for sickle cell for the first two columns and then we start having more work to do. We are still open to input from the committee even before we are ready to present to the full committee, we need lots more work on the potential data sources. And the last column is how we would relate this back to that paper by Cindy.

Looking at direct outcomes around information around access to care and information about other key outcomes. As an example on the next slide, you can see how you might --

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In newborn screening and sickle cell, major justification is the potential life-saving -- the well-documented life-saving effect of prophylactic penicillin in infants with sickle cell, so that would be the justification or one of the justifications for newborn screening for sickle cell and if you were to look at what might be potential measures of outcome, you can look at what percentages of children around penicillin at various different ages and how children. How quickly do they get on penicillin and how quickly -- they kept theirs? Looking at data sources, can answers be found to those questions and the newborn screening program or something called the RUSP data? And not a sickle cell expert, but one of the things that was interesting is that this is the kind of information that we know that some of the funded programs were collecting, but some of the limitations of that data are that these were time-limited projects. They do not, data from every state on we do not know they collect data from every child, so a very important questions and we are trying to gather outcome data to answer the question, are we achieving our goals for better outcome as a result of newborn screening if we have to pay careful attention to the denominator?

Are we getting outcome data on all children, or only on children who are participating in a research study, for example?

That is where we are in our current draft, and our plans for this project that we specifically have asked for the presentation to begin our meeting from, as I mentioned already, from Sue Berry and Amy, we are now asking for some assistance, which I think Sue will be able to provide, to compare our current draft framework with the data elements that are currently part of the data collection and the regional collaborative project. Along with that an additional input from our subcommittee, we just revised the framework yesterday and we will continue to revise it. We are asking our committee members, while being very clear that this is a draft, but with a goal to see how much we can harmonize future efforts in data collection, asking people to get input from other colleagues and stakeholders and bring that information back to revise framework. We are working on and depending on all of our committee members, and particularly input from Alan, to pay attention to the developments in electronic health records.

We are beginning to explore what the gaps in data sources are, including attention to that issue of the denominator, and our plan is to bring a revised framework that draft paper to, I hope, next meeting, but it is possible that it may take us until the fall.

That project presently asked for an update on, and you know that our subcommittee has been very interested, is the issues of medical foods. We had an update from Christine Brown with the advocacy community, and it was a little saddening. They have had a reception at the federal level, and people are willing to talk to them. But it was made clear that there is no federal authority to require that states cover medical foods, and changes in healthcare delivery that are currently in process have made it very clear that states have the authority to make those decisions but not only that, this is very interesting and frightening, with the new processes and plans, there will not be any right of appeal if medical food is not covered by state benchmark plans, but medical necessity will not matter. There will be no right of appeal. The efficacy community is planning to continue work with Congress to reintroduce the medical foods equity act that was introduced in the last Congress. We also had an update from Kathy, from the Office of Nutritional Supplements working on both some very interesting questions of how to better design and how to better get more good evidence-based research on medical foods and other nutritional supplements. And although NIH cannot work directly on this, they are 0providing technical support for professional organizations, working on evidence-based guidelines and understanding and providing technical support for some of the system issues that might impact access in ways that might have to do with definitions or coding. It has been very useful, and also just a final update on the medical foods project that the committee has heard about before, looking at access to medical foods and nutritional supplements, and that paper is impressed.

Future for the subcommittee, you heard from Chris the timeline for the point of care and lessons learned project. The timeline for the framework for outcomes project which is I think possibly more likely to be in the fall, that we have an ongoing interest in medical foods and no active subcommittee projects. I didn't want to end by saying that the last full committee meeting, the subcommittee asked for whether the topic for a future full committee meeting could be the impact of the ACA and essential health benefits decisions on the population of children with terrible conditions, and we could check to be sure with Sara but it is my understanding that they are currently planning to have such a presentation at the next meeting and working on what that presentation might entail, whether it might be an individual or a panel, but lots of thought going into that. Our subcommittee is looking forward to hearing that, and we are beginning to think and hope to discuss in the future, with the full committee, whether some of our current projects might lead to questions that you may want to have the subcommittee look at in the future as we begin to see the light at the end of the tunnel for our current project. With that I think we can open to questions unless Chris, you have anything to add.

The point of the medical foods, there is not a federal response of states needs to pay attention to their proposed state court benefit package. You have to look at that, whether it is included in that.

I could add, that is, many states are like Maryland and they are working with such programs, that there is no avenue to make a request for any specific benefit to be included because they were just

looking at benchmark programs. They will either be in the benchmark program or not there are other things that affected the larger numbers of people that let choosing benchmark program.

I do not want to disagree with you, but I do want to make it clear that in some states there is no avenue to do that.

Let's open over the phone lines and we will take any questions.

I have one question. I may have missed how that people came together, but I would question the term justification, and I think you said it is pretty clearly justified in the literature. I am not sure that is the kind of data that you're looking for in the other columns. Is probably more like quality improvement to make sure that they are getting penicillin initiated at the right times and that sort of thing.

This is Carol, thank you. I believe that is the kind of information we are looking for because we would not want anyone to -- the word justification was intended to help populate the second column with what is the reason that we are screening in the first place? But I think you're pointing out that as a result, if you have the word justification as a title, and that you're looking at the percent of data, it looks like the percentage of children on penicillin that justifies the screening and we did not intend that. We need those kinds of comments do make sure that we are representing something in a way that can be misunderstood.

I thought the others looked okay, because I glanced up quickly, but obviously you focus your attention on that one so it struck me that it was not really justification.

The justification was only supposed to help populate the second column and that is important, we will have to think about how to remain that.

My second comment relates to the work you wanted to do to identify gaps in data sources. I would suggest that you also add to that, not just the fact that you there are gaps in data sources, natural gas and your ability to access data sources that you even know are out there. We have been working on our own data sharing and access policies; they are largely deferred to our working with grantees around the sharing aspects that is built into their grand when they got funded to work with the program. I think you will find that there is an interesting issue, not just where you think it is but in whether you can access it.

Excellent point, absolutely.

Additional questions or comments?

Getting back to the point of coverage, right now is where states are debating their health benefit package that applies primarily to the exchange plans, but certainly is an important part of trying to get into -- if you can individually, but you also communicated with the federal government decides not to be involved in the potential health benefits package discussion, so that is where we are right now. Right now, you will end up with the same kind of coverage that we currently have, possibly sort of a higher tier or plan, and maybe the willingness to cover those types of things.

One comment I would make is that it also -- to follow what happens as this go into place and document limitations of essential benefit packages for special needs populations. If they are there, which we think they will be.

This is Carol, that is a very interesting point. We certainly could end up with stories and examples, but I wonder if there might be -- there would have to be done pretty quickly that I wonder if there might be some way to pull together a different framework for trying to ask, but the percentage of denials of coverage for medically necessary therapies or evaluation before and after the institution of this new essential health benefits package. We would have to get in that together pretty quickly.

Additional questions?

While that is going on, any additional questions?

If not, I think that will --

A public comment. I am happy to read this if you like. Christine Brown, all the states have submitted their benchmark plans and are posted on the CMS website.

Thank you.

That is going to conclude in the subcommittee report. I thank the subcommittees and the chairs for their effort. This is been very productive. I also thank the committee members and liaisons of organizational representative speakers. If there are any challenging -- this is been a challenging meeting, and it appears that you all have done your best to stay tuned while watching your computers, so I really appreciate that. But I do think there are clearly some serious differences between having a meeting where we are all the same room and having a meeting such as this. If any of you have specific comments and you want to make, please send them to me and we will do our best to try to make the arguments about the importance of being face-to-face. So we will try to do that.

Lastly, all of you know this is Sara's last meeting. At the end of February, she is leaving to move to California. I just wanted to know how helpful she has been. I don't think there's anyone who knows her so that are or how to get things done and how to keep things organized. So I have felt very comfortable with her as a designated official. We want to thank you for everything you have done and thank you and good luck as you had to the next part of your career.

Are all the phones open? Let's see if we can get a round of applause on the Internet for Sara because this is the last meeting for her.

[applause]

That will conclude the meeting, there is no additional business so thank you all very much and hopefully we will figure out whether we can get things together to have a meeting in April --

Congress to any potential delay they have. We look forward to that possible meeting, so thank you all again. We will talk to you soon.

Thank you, Sara.

[event concluded]