DACHDNC WEBINAR – FULL COMMITTEE DAY 2

Dr. Bocchini: . . . of the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. I hope everyone had a chance to kind of rest up and prepare for today's presentations, both this morning and this afternoon. I have a couple of housekeeping notes before we begin. For committee members, remember sound will be coming through your phone line, so please make sure you have your computer speakers turned off. Hold questions and comments until the end of each presentation and committee members and organization representatives please use the raise hand feature in Adobe Connect. I think that worked very well yesterday. We'd like to continue to do that. When invited to speak, state your name each time. Also please speak clearly to ensure proper recording for the committee transcript and the minutes. Press star zero if you have any problems with your phone line. For the members of the public, sound will be coming through your computer speakers, so please make sure you have your computer speakers turned on. I will now conduct a roll call. Don Bailey?

Dr. Bailey: Here.

Dr. Bocchini: I'm here. Jeff Botkin?

Dr. Botkin: Here.

Dr. Bocchini: Carla Cuthbert for Coleen Boyle?

Dr. Cuthbert: I'm here.

Dr. Bocchini: Denise Dougherty? Charlie Homer?

Mr. Homer: Here.

Dr. Bocchini: Kelli Kelm?

Dr. Kelm: Here.

Dr. Bocchini: Fred Lorey. It's my understanding that Fred will be able to join us sometime after the beginning of the session. Michael Lu?

Dr. Lu: Here.

Dr. Bocchini: Steve McDonough?

Dr. McDonough: Here.

Dr. Bocchini: Dieter Matern?

Dr. Matern: Here.

Dr. Bocchini: Melissa Parisi?

Dr. Parisi: Here.

Dr. Bocchini: Alexis Thompson?

Dr. Thompson: Here.

Dr. Bocchini: Cathy Wicklund?

Ms. Wicklund: Here.

Dr. Bocchini: Andrea Williams?

Ms. Williams: Here.

Dr. Bocchini: And Debi Sarkar.

Ms. Sarkar: Here.

Dr. Bocchini: And then once again Denise Dougherty? All right. Now for the organizational representatives in attendance, Freddie Chen? Beth Tarini?

Dr. Tarini: Here.

Dr. Bocchini: Michael Watson?

Dr. Watson: Here.

Dr. Bocchini: Mindy Saraco?

Ms. Saraco: Here.

Dr. Bocchini: Kate Taft? Susan Tanksley?

Dr. Tanksley: Here.

Dr. Bocchini: Chris Kus?

Dr. Kus: Here.

Dr. Bocchini: Adam Kanis?

Dr. Kanis: Here.

Dr. Bocchini: Natasha Bonhomme?

Ms. Bonhomme: Here.

Dr. Bocchini: Ed McCabe?

Dr. McCabe: I'm here.

Dr. Bocchini: Cate Walsh Vockley?

Ms. Vockley: Here.

Dr. Bocchini: And Carol Greene.

Dr. Greene: Here.

Dr. Bocchini: All right. Thank you all very much.

Dr. Chen: No, it's Freddie Chen. I'm here. I just hit the wrong button. Sorry.

Dr. Bocchini: All right. Thank you, Freddie. So this morning we're going to start with a presentation on newborn screening specimen transport, an update, and we're going to modify this presentation a little bit. As you know, the background of this is that a parent indicated to us at a September meeting that there was a delayed diagnosis of a metabolic disorder in her child that led the committee to make the decision to look into this to see if it was an isolated incident or whether there were additional issues related to timing of specimen transport. So we charged APHL and the CDC to work with us to initiate a survey to evaluate timeliness of the receipt of specimens across the state. Subsequent to that there was a series of articles published in the Milwaukee Journal Sentinel indicating that there were problems at least in the reports from states that participated in a survey in timely receipt of specimens and – and turnaround time for – for data. So today we're going to hear from Susan Tanksley, who is co-chair of the Laboratory Standards and Procedures Subcommittee. She's an organizational representative for the Association of Public Health Laboratories. She is going to give us a preliminary report on the – on – on the data that they have found, but since this was discussed in detail at the Laboratory Standards and Procedures Subcommittee the chair of that committee, Kellie Kelm, will follow Susan's presentation with some summary of the discussion and with some recommendations to come for the full committee for discussion subsequent to that. So the rest of the subcommittee report will occur this afternoon. So Susan, if you're ready, we'll turn this over to you.

Dr. Tanksley: Good morning, everyone, and thank you for allowing us to give a longer version of our subcommittee report. As Dr. Bocchini mentioned, we were tasked during the last secretary – the last Discretionary Advisory Committee meeting to look further into this issue and so we're going to give a report today based on what we've done thus far and discussions held in the subcommittee meeting yesterday. Next slide, please. So the entire point of newborn screening is that we identify life-threatening illness – illnesses before symptoms begin. So in order to do that, we have to have basically everything work right throughout the entire newborn screening

system. The first part of that is – is dispensing collection itself and getting that specimen, a good specimen, to the laboratory, having it tested in time, reported in time and treatment initiated in time. So Dr. Bocchini mentioned that – that this charge was based on public comments in the September meeting. So we were tasked with looking into issues related to the timely handing of samples and whether the committee should make recommendations on this issue and if you recall from public comment yesterday, we had two mothers who both commented on this specific subject as well. Next slide, please. This falls under Priority B for our subcommittee, which is to provide guidance for state newborn screening programs in making decisions about lab implementation, integration, follow up and quality assurance. Next slide, please. So our approach was to first gather background information and as Dr. Bocchini mentioned, CDC and APHL were charged with data collection. APHL surveyed the states and we'll give preliminary data from that survey this morning which was presented by Jelili Ojodu yesterday during the subcommittee meeting. We were also tasked with reviewing previous recommendations that had been made. So looking back at the 2005 ACMG report that was published in 2006 also considering COSI guidelines and – and other guidelines such as CAP newborn screening checklist. That's another resource that we could still look into. We had the committee discussion, the – sorry, the subcommittee discussion yesterday and then at the end of the presentation, Kellie will be giving a possible proposal for moving forward with this. Next slide, please. So as I mentioned, Jelili Ojodu from APHL gave preliminary results from their survey. Next slide, please. So the – it was a web-based survey that was created and initiated in – in December. The timeframe for completing the survey was very short and it was over the holidays, so December 19 and with a due date of January 6. Within that timeframe, 32 states responded to the survey and there are six others who are either close to or have already completed the survey, but their data is not included due to the fact that it was received after that – that deadline. There were quality assurance and data control checks performed on the data that was provided. However some of the data – some states could not provide the data exactly as it was requested. Next slide, please. So we'll go through some of – some of the results for that survey now. So the first question asked was basically how does your state or how are specimens transported in your state from birthing hospitals to the newborn screening laboratory? So 32 states who responded and states could respond with multiple answers on this question. 18 of those used courier service. 19 used overnight delivery service. 20 used U.S. Mail and 8 others were mentioned as well. Next slide. The next question, does your – does your state have a recommended time period for when specimens should be received by the newborn screening programs from the hospitals? This is basically is there a policy, a guideline, a law, a recommendation that is made from the newborn screening program or from the state to the healthcare provider. So 62% had a policy or practice or recommendation

or law in place as to when specimens should be received. 19% had no such policy or procedure. 19% of the states indicated that they had a policy or practice or law related to when the specimens should be sent, so that would be sent from the health care facility to the laboratory. Next slide, please. In regards to whether states actually have regulatory authority in order to fine or sanction hospitals who don't comply with laws in regards to newborn screening, specifically for sending samples to the lab, 24 states responded. Of that, only 17% of the states, which I believe Jelili said was four states, actually had laws in place that allowed them to have regulatory authority over the – over the healthcare providers. Next slide, please. Okay. In regards to states – you know, in regards to what states are doing to provide feedback back to healthcare facilities, there were a series of questions asked and I apologize. Some of the words are garbled on the slide, but does your newborn screening program keep a record of transit performance by hospitals? 97% or 31 of the 32 states responded that they indeed kept a record of transit performance by the hospital. 91% of the states or 20 – 29 of the 32, actually review those transit performance times and of the 32, 94% or 30 of those have some mechanism of providing feedback to the birthing hospitals regarding transit times. So states are actively looking into this issue and providing that feedback to the healthcare providers. Next slide, please. The types of feedback that might be given might be report cards. Some states call those quality reports. They may be given quality improvement tools, so some mechanism to help them – to help the healthcare provider perhaps learn a best practice or – or – or how to improve their performance through educational materials, through newsletters such as a newborn screening program newsletter, or through feedback on a one-to-one basis, maybe via phone, possibly in person. Next slide, please. In regards to laboratory operating hours, 12 of the 32 respondents indicated that their labs are consistently closed on Saturdays and Sundays. The other 20 responded that their labs are open at least – that their lab or labs are open at least six days a week and 4 of the 20 respondents only receive specimens that do no further testing activity on the Saturday or the Sunday. Next slide, please. Six laboratories of those 12 who are currently closed on a Saturday or Sunday are considering opening at least one more day a week, to be open at least six days a week within the next one to two years. Next slide, please. In regards to follow up because if you have a test result and it doesn't get reported out, nothing actionable can be done with that test result so the follow up operating hours in regards to weekends, 17 of 28% of respondents are consistently closed on Saturdays and Sundays, 11 of 28 or 39% are open at least six days a week and 65% responded that they offer after hours paging or on-call services on Saturdays or Sundays. Next slide, please. So through the NewSTEPs program several quality indicators, eight listed here, have been proposed and will be included in the NewSTEPs database. This was mentioned in the talk yesterday on NewSTEPs by Jelili and Marci. Quality indicator number five speaks

specifically to these timing issues, so the time elapsed from birth to screening, the time to follow up testing, the time to confirmed diagnosis and these can be broken down into even further detail. So that data will be the data that states are requested to submit to the NewSTEPs database. That will be published or – or that will be done on an annual basis, so after – so for example we would – in 2014, we would be submitting data for the year 2013 to show our times for 2013. Next slide, please. All respondents to survey did note that the timeframe from birth to specimen collection was in the 24 to 48 hour timeframe, so the 32 that responded, all were collecting or at least the recommended timeframe for collection was within the 24 to 48 hour time frame. Next slide, please. In regards to the question what is the median time and days from specimen collection to receipt by the laboratory for your state, there were 17 respondents. Of those, 6% were received in the specimens – the median of that timing was less than one day. Another 6% was between one and two days, 41% between two and three days and 47% had a median of three days. Additional data was requested in the survey. However, there were not enough states that had responded in order to break those times out further. Data collection is a difficult thing if you don't have a system set up to accurately – accurately collect the information and easily pull the system from – pull these data from the information system. Next slide, please. So as noted, there were limitations of the survey to the timeframe for the response was short and it was during the holidays. Some of the data, as I just mentioned, was incomplete. Some questions were – were left to the interpretation of the person who answered the survey question and then another afterthought from the survey was that had the definitions been included for the quality indicators, it could have given greater clarity. APHL is still seeking to collect the rest of the – the data from the states who haven't submitted yet and they will be contacting those states. The goal is to have 100% participation but at this point, as I mentioned, there were 32 states who had responded to the survey. Next slide, please. Our next presenter was Mike Watson and he presented on the ACMG standards for newborn screening and their oversight. Next slide, please. So as probably everyone on this phone call knows, many many years ago now in 2001, HRSA charged the American College of Medical Genetics – Genetics with evaluating the scientific and medical information related to screening for – for specific conditions and to make recommendations based on the evidence. A very large expert group was convened beginning in December 2002 and results were reviewed by an independent newborn screening external review group. Out of that came the newborn screening toward a uniform screening panel and system which sometimes referred to as the 2005 report, however it was published in 2006. It is a very well-known report in newborn screening. Next slide, please. And it was divided into two sections. So Section 1 is – was about the uniform newborn screening panel and in almost all citings of this report, that is what's being cited. So people are talking about the report and how it

established a uniform newborn screening program. Less well known is Section 2, which was about the newborn screening system itself. The last slide – thank you. So it focused on the newborn – Section 2 focused on the newborn screening system with program evaluation, a section on cost effective analysis, a section on information gaps and research – a research agenda and future needs. Next slide, please. At the – in Section 2, there were ten program standards that were recommended and we're going to focus today on the ones that specifically speak to turnaround and how we might be – well, and – and oversight for that. So the recommendation is – I think it's Recommendation Number 4 of those, turnaround time and reporting screen negative results should be improved, so highlighted three different recommendations within this. Essentially all results should be available less than five days after the blood sampling or the specimen collection. The second recommendation from that – most results should be available within two days of the specimen arriving in the laboratory and the third – specimens should arrive within the laboratories within three days of the collection. If you – if you break that down and – and you – you begin to add things up, if specimen transit time takes three days, it's virtually impossible to get all of those results out within five days. So it's very, very difficult. So in a separate section of the report, it actually talks about specimens should arrive in the laboratories within 24 hours of collection. So that's something we can discuss later. Next slide, please. Another standard that was mentioned in the report was that hospitals and formally JACO with the Joint Commission have significant roles to play and standards need to be developed to improve quality minimizers and to facilitate tracking of newborns requiring active participation in testing follow up. Acknowledging the very, very significant role that hospitals have in specimen collection, in getting the results – I'm sorry, in getting the specimens to the lab, in having accurate data to submit with the specimen, tracking those specimens to ensure that they're not only received in the lab, but that results are received back and if there is a result that needs to be followed up, that they participate in that process. Next slide, please. So as a consequence to that or soon after that, ACMG initiated discussions with the Joint Commission and they had multiple discussions over a several-year period and they did an extensive – did extensive research on legal liabilities associated with newborn screening activities which was completed in about 2008. However, it is – perhaps it's time again now, and we talked about this yesterday, to reinitiate that conversation and bring the Joint Commission back into the conversation about possibly establishing standards related to newborn screening for hospitals. Next slide, please. And it was mentioned in Mike's report that states are in an awkward position in enforcing standards against hospitals, who they have to work with and they rely on for program delivery. So not only are the hospitals a customer in regards to who is submitting the – the samples to the laboratory, but they also – the states also need to work with hospitals and make sure that they can reconnect with the patients

whenever there are critical results that need to be reported out. And again a possible next step is to reengage the Joint Commission on development of standards for hospitals. Next slide, please. As I mentioned, the – the ACMG report talked about newborn screening as a system and I mentioned in the very beginning that everything in the system has to work well together in order to achieve timely newborn screening result and ultimately timely treatment for those who are diagnosed with newborn screening condition and there are six components that are key to a good newborn screening system. The first one is education, which needs to occur throughout the process, beginning in the prenatal period and basically touching everyone who might be part of the newborn screening process. The screening itself, which includes specimen collection and the testing, follow up of any out of range result and reporting those results appropriately and in a timely manner, the diagnostic confirmation of those newborn screening results. It was mentioned many times yesterday during the sickle cell trait presentation about how newborn screening is a screen and it is not a diagnostic test and that confirmation is critical. Management of the patients who have newborn screening disorders throughout their lifetime and then finally program evaluation and continuous quality improvement, so looking back at the newborn screening programs themselves, the newborn screening systems and trying to improve all aspects of that system. Next slide, please. So what are the issues and where are they occurring and if we are able to measure each detailed step in the process, then that would allow us to pinpoint where breakdowns have occurred and the diagram at the bottom of this slide is a very simple – very, very simplistic view of newborn screening and it doesn't always work this way. But if you consider each – each step in newborn screening as a discrete process, then you can measure each of those as a discrete process as long as you have a way to collect that data accurately and in a queryable form, so in a way that you can actually pull the data easily from the system so that you can easily analyze that data. Newborn screening is made up of the pre-analytic phase which starts when the specimen is collected through the time it arrives at the laboratory, the analytic which is the shortest timeframe which is the testing timeframe and then post-analytic which begins immediately with reporting out of the newborn screening results, going through treatment intervention and – and all the way through management of that patient as well. So there are some key measurements that you can take. The timing of the collection, so at what point in the baby's life? Generally this is recognized to be 24 to 48 hours. The transit, time, which I'll define here as the time from specimen collection to the time that specimen is received in the laboratory for testing, the time to result or time to a report which you could measure from birth to screen results or you could measure from specimen collection to screen results or you could even measure it from the time of receipt in the lab to the time of reporting that result, and then finally the time to treatment which for all intents and purposes is – is really our most

important time point because that's the one that really impacts the baby and – and is where you add all these steps together, so from the birth of the child to treatment of that disorder. Next slide, please. So as we mentioned, the 2005 report newborn screening towards uniform screening panel and system, there were actually two points of report. So on Page 80 it was mentioned that the suggested transport time for courier services that allow that these two have receipt at the laboratory within 24 hours. There was also a time point mentioned for reporting of life threatening or time sensitive disorders to be within a few days after birth. So it was noted that it is desirable to initiate specimen processing within 24 hours of specimen receipt in the laboratory with a five-day turnaround time between birth and the availability of those test results. So that recommendation is a little different than the recommendation that – in those ten recommendations at the end of that section of the report in that this is for the really time sensitive disorders and the – the definition being from the time of birth to the availability of the test results, whereas the time for all results is within five days from specimen collection to the result report. Next slide, please. So based on the ACMG report, there were some recommended timeframes. The timing of collection wasn't a specific recommendation within that report. However, there was mention of data and those collected before 24 hours of age, those collected after 48 hours, although it didn't specifically recommend collection at 24 to 48 hours of life. Transit time, as I mentioned, there were two different recommendations. So one being receive at the lab within 24 hours of collection and the other being within three days of collection, and then the time to result for the critical results is within five days of life, so that would be from birth to the results of those critical, time sensitive disorders and then the time to result for all results would be within five days of collection based on those recommendations. Next slide, please. So after the presentations, we – we did have a little bit of time and so I'm going to highlight some of our key points of our discussion and then we'll move into our proposal for the committee. So some of the key – key points were that it is incredibly important to have good quality samples in order to achieve timely test results. So if you have a sample that is not good quality and it cannot be tested, then you have lost that window of opportunity in order to catch a disorder early because that requires a recollection of the specimen. Access to data is key. I've talked several times about – about data and the need to have a good data collection method, a good data collection system so that you can use your raw data to actually analyze results and not just look at averages or medians because those – those really hide your outliers which are your concerns. Education is needed throughout the entire healthcare system, so anyone who might come into contact with newborn screening needs to know how important and how timely newborn screening needs to be to be effective. It was mentioned that the time sensitive nature of newborn screening may not reach all levels of the healthcare system and specifically what was mentioned was that newborn screening is a send out

in a hospital lab and so it's possible that the people who are in the lab might not have knowledge of that time sensitive nature. So we need to make sure we're educating everyone in the – in that hospital system who may be touching newborn screening. Dr. McCabe mentioned that the March of Dimes is convening a consortium and I think it was about ten different organizations at this point to discuss the issues of the timeliness of newborn screening and there was discussion about consolidating those efforts so that all the players could be in the room and so if – if we have multiple groups who are working independently on the same issues, then we're duplicating efforts that we really need to work together and consolidate those efforts. It's also – it was also mentioned that there's an appendix to the ACMG report that we really need to dive into deeper and so that's a future need as well to review that appendix further. Next slide, please. And then the other points were that we – we have state examples of really good systems with fast turnaround and Iowa was specifically mentioned and Stan Berber talked about how they had gathered data and adjusted their staffing and testing based on that data, so we actually analyzed when babies are born in the state of Iowa and looked and saw that most of those babies were born mid to the end of the week, and therefore specimen collection would be happening towards the end of the week or on the weekend and so he felt the urgent need that every day that these – that they needed – the lab itself needed to be open and they needed to have a courier service that would also pick up every day of the week and deliver every day of the week. It was also mentioned that during Hurricane Katrina, there was some prioritization of testing that had to be made, so what is time sensitive and pushing that testing forward so that those very time sensitive disorders could be reported out more quickly. I think in general that something that's done on a daily basis in many, many newborn screening laboratories so that the most urgent – the results that are needed most urgently can get out the most quickly. We discussed the need to gather and share best practices. It was also mentioned that since 2005 test platforms have been added, they've changed and new conditions have been added to the panel. So the point was brought up that we should probably reexamine recommendations, the recommendations for timing that were made and – and determine do these recommendations still make sense? Do we need to change them or are there additional recommendations that need to be made? Next slide, please. So I thank you for your attention. I'm going to turn this over to Kellie now so she can talk about the next steps.

Dr. Kelm: Good morning and thank you, Susan. That was – I felt that [unintelligible] quite well. So we have based on the committee's discussion yesterday and – and other discussions led to proposals at the [unintelligible] that may be for our to consider and discuss some potential recommendations for the committee and – and future work for a subcommittee. Next slide, please. So number one, potential – I will move to reaffirm the recommendations in the PR group five reports that Susan just went over and urge states to

work toward meeting the recommended timeframes and as part of that, I think the subcommittee would like to continue to work with stakeholders or members to gather primary data as well as to be mentioned some of the best practices that states have used to improve their timeliness. I think that would be a great new source for everyone. Number two, as Susan mentioned, so give some special consideration to [unintelligible] to new technologies and conditions that have been added since 2005 [unintelligible] report and discuss and return with other recommendations that need to be updated or clarified and last charge accordingly independent efforts to address the timeliness of newborn screening issues as far as we discussed [unintelligible], you know, metro [unintelligible] consortiums and meeting. We just want to make sure that everybody's coordinated and working together to avoid duplication of efforts. So I believe that is it. Our next slide, this is questions that I think if we can leave this slide up and turn it over to Dr. Bocchini to – to help lead the discussion.

Dr. Bocchini: Thanks, Kellie and Susan. Thank you very much. We appreciate the work that you've done confirming to this point. This presentation now is now open for discussion and for questions and comments from first the committee. So again, let's use the hands up icon and begin the conversation. First we have Steven McDonough.

Dr. McDonough: Thank you for an excellent presentation. I think I would like a stronger statement coming out of the Advisory Committee. Anyway, I'd like to thank the parents who brought this to our attention and the investigator journalism of the Milwaukee Journal Sentinel. I live in North Dakota out in the middle of nowhere and I [unintelligible] a metabolic screening and when I've been on call, I have been – received a notification on a Saturday afternoon that a child had an abnormal newborn metabolic screen and was – the child was like two or three days of age, so I can know that the service that Iowa provides us is excellent. There was a little scrambling on my part to get the child taken care of, but we had that child admitted that same day. So I know the system can work if it's done well. I want to thank Dr. Bocchini for his comments on this issue. I also want to bring up a point that I know that MCH is currently looking at straw objectives going forward in the maternal child health program. I think it's important that newborn screening have an objective and would suggest the timeliness of collection perhaps be added to help MCH programs work with public health labs to get more timely . . .

Dr. Bocchini: Steve, could you speak up a little bit more? The – the transcriber is unable to hear you. Sorry.

Dr. McDonough: Can't hear anything I'm saying?

Dr. Bocchini: Well, I – I 'm not sure they're – they're – they're – they're missing some of the comments, so . . .

Dr. McDonough: Okay.

Dr. Bocchini: . . . speak up a bit.

Dr. McDonough: I'm talking too fast, perhaps. So anyway, the points – the main point I would like to make is I think it's a very important issue that we need to do better. I think it would be appropriate for the committee to make a recommendation to the secretary to send out to the states on timeliness rather than just endorsing a ACMG, you know, recommendations from a few years ago. I also want to – the point they're going to have is in the MCH straw objectives that are coming up. I think newborn screening should have one of them and then suggesting that timeliness of collection be considered for that. So those are the comments I have.

Dr. Bocchini: Thank you. Next, Charlie Homer.

Dr. Homer: Yes, thank you. I similarly wanted to thank the presenters. I thought that was extremely clear and also glad that we have the opportunity to discuss this. I want to reinforce that sense of I think we can have stronger recommendations than the ones that are presented here. In a sense what looks to me is that 2005's criteria, we almost should view those as a floor for recommendations. I think we should always be striving to continuously improve, not surprisingly given my work. I – I appreciated and agree fully that we should be tracking the outliers, for example the proportion that are received over a certain amount of time rather than the median which I think is not going to be sensitive to what's most important. One question I guess I'd ask just for point of clarification is what regulatory – what the – how state labs get approved, whether there is a regulatory national authorization either through APHL or otherwise and whether that's their vehicle for, for example, addressing issues such as staffing a number of hours that the program is open, what their internal processes are. It seems to me that that's something that at a national level we'd like to see some state authority for. I was a little confused as well by the comment that says it's difficult for states to both regulate and cooperate. I think everybody on the phone that's from a public health department knows that that's a – a dance and a balancing act that public health departments and state agencies in general have to do all the time and I don't think we should shy away from that sort of dual responsibility of both regulating and cooperating. Those are all my comments for now, but again thank you. I think this is extremely timely and I'm looking forward to our committee taking strong action.

Dr. Tanksley: Dr. Bocchini, this is Susan. May I respond?

Dr. Bocchini: Yes. Please do, Susan.

Dr. Tanksley: In regards to enforcement on the state laboratories, state – or newborn screening is a state-based activity and therefore other than the regulations such as CAP or CLIA regulations, there is no regulatory enforcement. However, the – unless it's at a state level, however the NewSTEPs program does have an evaluation team and that is something – it was mentioned yesterday by Jelili and Marci, but that is – that is something that states can request and those evaluations are very helpful because they look at the broad spectrum of newborn screening, the system within the state, and recommendations are made based on that evaluation and then those evaluations are very helpful for the state to be able to make changes that they feel are necessary in order to improve newborn screening. Texas previously had one in 2005 from NNSGRC who was the previous technical resource center for newborn screening and – and that was extremely helpful for our program and – and really helped us to improve, so it's an external review by someone else. It's not a regulatory authority. But it – it is helpful in order for you as a state to get the resources that you need because it's – it's a different body saying you need to improve on something.

Dr. Bocchini: Thank you. Thank you, Susan. The next person is Jeff Botkin followed by Cathy Wicklund.

Dr. Botkin: Yes. Thanks for the presentations and it's been good to see how quickly folks have been motivated to pick up on this . . .

Dr. Bocchini: Jeff, can you speak up a bit?

Dr. Botkin: Sure. How about – how's that sound?

Dr. Bocchini: Not much better.

Dr. Botkin: Okay.

Dr. Bocchini: There you go. That's better.

Dr. Botkin: All right. So I have sort of two questions. It seems to me that two issues that as a non-lab or program person seem to be obvious issues are the lab being open over the weekend and courier services. So my first question, I don't probably really understand what being open means and so do we have data that clearly indicates that the lab hours are associated with the reporting time? And then my second question is who covers the cost of the courier services? Is that part of the kit fee for hospitals or do they pay separately for that service? Thanks.

Dr. Bocchini: Susan, can you address those?

Dr. Tanksley: Yes. Yes. So first question in regards to lab hours and whether that's associated with reporting times. Generally it is associated with reporting times, so I showed two different slides, one with percentage of states that were open or closed and the second with percentage of states that had follow up that was basically available or not on Saturday. So some – some labs report the results out themselves. Other labs use follow up staff to report out those results. So I'm going to make a general statement, though I don't have data tying those two exactly together. It is something that could be asked on a future survey, but in general if a lab is reporting out – is – sorry – is testing and getting results on a Saturday, if there are critical results they are being reported out. The less time sensitive results may not be being reported out and I can speak from Texas experience in regards to that. We are open on Saturdays. We report out the critical results and we have a list of prioritized disorders of what gets reported out on a Saturday. However, the less time sensitive conditions, those results are followed up then on Monday. In regards to your second question as to who covers the cost of courier, that is – there actually was a slide in regards to how that's paid for. In some states, the hospitals or – or the – the submitter pays for the courier. In some states it's paid for – it's included in the newborn screening fee and it may also be paid for by the state itself or by the program itself and it's – it's probably a mixed model in some of those states as well. Did that answer your question?

Dr. Botkin: Yes. Thank you.

Dr. Bocchini: Jeff, did you have a follow up question that went with that?

Dr. Botkin: No, not at this point. Thanks. I think that's very good.

Dr. Bocchini: Okay. Thanks. Cathy Wicklund?

Ms. Wicklund: Yes, thank you and thank you guys for your presentation. My question is kind of similar to Jeff's. I was wondering if you in the survey it had any like open text boxes, you may have that, that you could get a better idea form the state perspective, like the – the rationale behind the hours or, you know, being closed on weekends, the barriers that exist maybe from, you know, extending hours or opening their times or if you have any insight into that?

Dr. Tanksley: Yes. So there were open text boxes in some portions of the survey, but not in others, and there was kind of a – at one point there was a question about barriers and it was a multiple choice – it was a multiple choice answer followed by an other with an open text box and so I don't have those slides directly in front of me so I'm trying to recall this from memory at this point. Staffing is an issue. Funds, I – I wish I had the slides in front of me. I'll – I'll try to pull those up so that I can answer it more thoroughly. I apologize.

Ms. Wicklund: That's all right. I – I'm sure it's the usual – usual culprits probably.

Dr. Bocchini: Okay. Now we have one of the fellow partners, Melissa Parisi.

Dr. Parisi: Hi. I just wanted to ask in this proposal as we're looking at on the slides, reaffirming the recommendation in the 2005 report, it – it seems like there's at least this one discrepancy that was pointed out between the recommended time frame between collection of a specimen and receipt in the labs. At one point it said three days, another point it said 24 hours. So I think before we reaffirm those recommendations, it might be worth clarifying which series of recommendations we're reaffirming and if necessary, number two should come before number one because if we're going to sort of reassess in light of new technologies and new conditions added, then maybe that process should come first. I'm not trying to slow things down, I'm just thinking from a logical perspective. And then finally, was there any discussion about lag periods of transport given temperature fluctuations and potential for samples to be either in very cold climates or very hot climates during certain times of the year and how that might degrade specimen integrity as a factor in the reliability of sample collection and testing?

Dr. Tanksley: So in regards to that – the question about temperature considerations and lag time and how it may impact specimen integrity, that was not part of our discussion. We really had a very limited time for a discussion and – and I speak for the subcommittee here, but I – I – I think we would all agree that we would all like more time to discuss this issue and look further into issues. Definitely in hot climates, specimen degradation is an issue and again, just speaking from Texas experience, when we added courier – a courier pilot for Texas [unintelligible] our false positive for galapticemia because we did have enzyme degradation from the heat. Kellie, would you like to speak to the other comment about the recommendations?

Dr. Kelm: Sure. I think the feelings from the committee, the subcommittee I apologize, was that although we agree that we are trusting that, you know, information would be useful or would be something the subcommittee should look at, that most of the recommendations that were in there would probably still be valid today in that they were goals that [unintelligible] should be meeting right now. I'm not sure if people felt that these would change very much honestly. We – we – we were talking but that the clarification would be something that we should do. But I do agree that given some of the potential discrepancies or differences in these recommendations that maybe we should as part of this discussion figure out, you know, if the committee wants to move forward with taking these recommendations and reaffirming them, that we specify which ones that we feel that the newborn screening [unintelligible] should meet right now.

Dr. Parisi: Great. Thank you.

Dr. Bocchini: Thank you, Kellie. I think we have Dieter Matern and then we have additional questions from our partners of liaisons. Dieter?

Dr. Matern: Yeah. Just a – I – I agree that the verbage might not be consistent in the [unintelligible] report but I think what – the committee could do is endorse the recommended timeframes in the previous slides where basically the time of collection is specified, the transit time as within 24 hours of collection and so on. Just – just for – for basically today until we have a more specific recommendation, I think that it – again it's a good starting point.

Dr. Bocchini: Dieter, that's a – appreciate that comment. It certainly gives the committee a chance to come out specifically with some guidance at the present time while the rest of the things are being looked at to provide potential approaches towards remedy of the situation. Ed McCabe?

Dr. McCabe: Yes. Thank you. I just wanted to qualify a little bit about what – about the consortium that was mentioned with the March of Dimes as a convener. First off, we've had only a single one-hour conference call which – which at the time included six organizations out of the current ten and it's important to recognize though that we're not only looking at timely – timeliness, it's – as one of the approaches that the March of Dimes composed was based on our op ed piece in the Milwaukee Journal Sentinel on November 23 with the title Baby Tests Require a Culture of Safety and we argued that it's a complex system with many vulnerabilities as has been pointed out here. [unintelligible] the person in the nursery only knows that they get a sample. It was obtained from the baby. They get it to the lab. They don't understand the larger context and – and the – the critical time sensitivity of the system. So we – we talked about that in there, but we're really looking at multiple vulnerabilities and trying to identify them prospectively using at least from the March of Dimes perspective the high reliability organization or HRO paradigm which is the basis for improving quality and safety that we've used in hospitals and actually came out of the aviation and nuclear energy industries. So I think I just want to make it clear, we're – see what – what was brought to our attention as a timeliness issue from the MJS could be an opportunity to look at vulnerabilities that are beyond just timeliness and – and inherent in any complex system.

Dr. Bocchini: Thank you, Ed. Next is Natasha Bonhomme.

Ms. Bonhomme: Great. Thank you very much. Thank you for the presentation, obviously very timely and a lot of really great data has been presented. I just wanted to make the comment that while I think it – we know that there are standards that are in place and that we know that there are, you know, suggestions that all of us who are part of the newborn screening

community are familiar with, that that data or information really isn't trickling down to the people who are actually in the nurseries and doing – doing the newborn screening and are responsible for putting the box in an envelope or what have you and sending them off. A key piece of the work of Babies First [unintelligible] while it's educating the public is also educating healthcare professionals and a lot of the work that we have done has been with those nurses who are in the nurseries to get them to really understand and to proper training around the fact that they're, you know, these specimens, you know, need to be collected in a certain amount of time and also sent back to the labs in quite a bit of time. So I think that it would be good as we're thinking about kind of not just recommendations but then also actual strategies to make an improvement, whatever we think that improvement should look like, to be really looking at the projects that have already taken place and been funded either on a smaller – larger scale to see, you know, what has worked and how are we actually going to be able to go because while this is definitely a lab issue, it also is an education issue and how do we educate the people who are actually collecting the specimens and really are the ones who have the control tube for the specimen and the [unintelligible] or – or don't. So I just encourage you to really think about that piece as well as we think about recommendations and strategies moving forward.

Dr. Bocchini: Thank you, Natasha. Carol Greene?

Dr. Greene: Thank you and again thanks for a great presentation and a – and an interesting discussion. I would like to emphasize the importance of JACO, the – the Joint Commission was mentioned earlier, and I think they are a really key player and I think that they should be encouraged to consider having a newborn screen marker or – or metric as a sentinel event and the reason I say that is I – I strongly endorse everything that's said about education. A couple of other activities that have happened – one of our master students studied the knowledge of nurses around Maryland with respect to newborn screen and it was pretty abysmal. The MMWR good laboratory practices for biochemical genetic testing, you know, whether it's in a biochemical lab or a newborn screening lab, there's a CE activity and one of the most dramatic comments in response to did you find this useful was I now understand and will collect newborn screens on time and so it's a continual effort to educate people. What we've found in our hospital is when every few years samples gets sent – one of our hospitals, every few years samples suddenly start arriving at the state health department later and that's because a new person is in send out and their mandate is to save money and so they start batching the specimens and sending the courier instead of daily, a couple of times a week. So this is a sentinel event and Joint Commission has a – a – a marker for hospitals. Then they will be compliant and then people will pay attention to the education. Otherwise it's incredibly important to the families but it is not high on the priority of the busy nursery or the laboratory to – to

educate all the new people who come into the system. So I think JACO should be encouraged to make this a sentinel event.

Dr. Bocchini: Thank you for your comment, Carol. Jeff, your name is up here again. Are – do you have an additional comment?

Dr. Botkin: No, I didn't.

Dr. Bocchini: Okay. Thank you. Are there any other additional questions or – or comments? If not, I think just to summarize, it – it sounds like there is a general agreement that the committee needs to make a strong statement. I would not want to make a strong statement and then have to revise it based on us reviewing or reassessing the – the – the timeliness of the – or the – the timeline for – for a specimen. So perhaps the best thing for us to do is to charge the subcommittee to look at the issue of reassessment within just to meet in between the meetings, to then bring the proposal to us to be looked at by the committee by email and then when that is finalized, we can put together a strong recommendation of which we would ask the secretary to remind the state that these are the recommendations of the – of the committee. So that would be one part of our response to this – this issue and then to ask the subcommittee to continue to work as a – within the range that it has of the – of the problems that it – it has determined and – and to further look at the analysis of the – of the survey to – to then see if we could come up with best practices and determine what other organizations we should be contacting and see if we could work with and – and – and – and also we could address the issue of involvement or – or reengagement with the Joint Commission and I think with American College of Medical Genetics with their prior work with that, that might be a good opportunity for us together to go back to the Joint Commission to begin to determine whether they would be interested in making the timeliness of newborn screening from the hospital side a core measure for – for hospitals. I'd also like to task the subcommittee for – also for looking at two other things to consider, the accountability from the laboratory side as well as the hospital side for processing, for obtaining and processing specimens appropriately to meet the timelines that we have and then to also look at transparency issue, to determine whether we could provide guidelines to the state or recommendations for how to address specific hospitals and – and – and – and in attempting to address the outliers and I think as Susan and others mentioned, I think we have a snapshot now of – with median times, but we do need to find a way within the states to recommend that – that outliers be identified in some way so that they could be addressed appropriately within the states. Are there other things that I've missed in – in my summation? Dieter, I see that you've raised your hand.

Dr. Matern: Yeah. I just wondered does that mean we will not in the – will you make part of this request to the subcommittee, put some verbage in there that we

feel that the – the recommendations in the 2005 report with a – with the timelines on the slide that we see in front of us should be considered right now the minimum standard and that of course for TTHD and all the point of care stuff, there – there might be differences?

Dr. Bocchini: At – I mean, I think that's essentially what we're – what we're going to do. I think we've, you know, I guess part of the reassessment is to determine based on the – the number of conditions being evaluated whether there are others that – that – that move into the – into the category of being high risk and – and critical testing so that we could indicate which of the ones that – that are – that are critical results so that they need to be done between five days of life versus those that – that can be reported within five days of collection. So that I – I would agree that – that that would – would separate out about hearing and – and – and other things that are not critical tests in terms of timeliness. Charlie Homer?

Dr. Homer: Yes, thanks. And you may have mentioned this. I simply wanted to reinforce Dr. McCabe's comment about using the framework of the high reliability organization and recognizing that this is a – a broad system for that improvement in bringing that home into safety science into the work and recommend that the subcommittee incorporate that strain in its deliberations.

Dr. Bocchini: I agree. Good point. Carol Greene?

Dr. Greene: Hi. I'm – I'm wondering if I might follow onto Dieter's question that it's going to be a little time to follow the – the strategy that you've outlined, which is I think the proper strategy. I wonder if it would be appropriate since the 2005 recommendations are not specific to individual tests and – and while there might be a need to make some elements slightly more stringent and there's going to be that review, I don't see any real down side to a strong statement from the committee today saying those 2005 recommendations that were carefully vetted and that the subcommittee says are still applicable as – as a minimum that the committee could say that is already out there. It needs to be followed as a minimum and the committee is working to see if it should be more stringent.

Dr. Bocchini: I don't have a problem with that approach if – if committee's in favor of pursuing this that way. I just wanted to not separate things and – and – and – and come up with a strong statement that then is followed by some modification, so that's – that was my only point. But if the committee's comfortable with these – this guidance that's up on the slide, we certainly can go forward with that part. Do I hear any comments from committee members related to that? Dieter?

Dr. Matern: I would support doing exactly what you just said and accepting this – what we see in front of us right now as the – the baseline of what should be

done right now, in particular of course the transit time from the birthplace to the – the screening laboratory.

Dr. Bocchini: I'm comfortable with that. If there is no objection to that from committee members, we will go ahead with that – with that portion of it and then task the subcommittee with the rest of the – of – of the guidance that we have back – we have provided them back.

Ms. Wicklund: Dr. Bocchini, this is Cathy.

Dr. Bocchini: Yes, Cathy?

Ms. Wicklund: Is there something in particular – I mean, I – I see your point in the sense that you don't want to come out too strong and then have to back off on a statement. Is there something in particular that you are concerned about that would indicate that that might happen?

Dr. Bocchini: Just that this was the floor and then we decided that we wanted to move to shorten the timeframe for anything, that that – that was my only issue, that if we tried to shorten the timeframe that we would have a strong statement about timing and then have to change that. That – that was my only concern, so if – if everybody who [inaudible] – I think if everybody's comfortable that this is the floor and that the adjustments would not be to the timeline, I'm comfortable with that.

Ms. Wicklund: Okay.

Dr. Tanksley: Dr. Bocchini?

Dr. Bocchini: Yes.

Dr. Tanksley: This is Susan. Just because there is that discrepancy for the transit time, could I read from those sections of the report so that the members could hear the exact wording and then that would just provide a tad bit more background to make sure it's 20 – within 24 versus within three?

Dr. Bocchini: Yeah, that'd be great. Go right ahead.

Dr. Tanksley: Okay. So on Page 80 of the report it's talking about kind of the survey data that was done and how specimens were at that time sent to the laboratories. The last sentence of that [unintelligible] is: It is suggested that specimens be transported by courier services that allow for receipt at the testing laboratories within 24 hours. Then on Page 93 of the report, which is where the ten recommendations are, as part of recommendation number four about turnaround time, the last statement of that is: Most results should be available within two days of the specimen arriving in the laboratory and specimens should arrive in the laboratories within three

days of collection. So I just wanted to provide more background on those – those two areas of the report. Thank you.

Dr. Bocchini: Thank you, Susan. Melissa Parisi?

Dr. Parisi: Well, I didn't have a comment specifically on that item, but is there a reason why there's no mention in this reaffirming the recommendations of the time of collection within 24 to 48 hours? I mean, I know that should be standard by now, but I wonder if it should also be included in the bullets.

Dr. Bocchini: That's a good point. I think that – that we should add that as a – to the – as the first bullet. Thank you. Dieter?

Dr. Matern: Yeah. I – I would bring us back to what we see on the slide in front of us and kind of ignore that there is some inconsistency in the ATMG report which had a lot of authors and a lot of pages, and so I think that they had an error in there. It's – it's just the way it is. But I think the subcommittee was comfortable with the fact that a newborn screening sample should reach the laboratory within 24 hours of collection.

Dr. Bocchini: Okay. I – I think that's – there's no question about that. I think that's fair. Okay. All right. Other questions or comments? Anybody opposed to going forward? Steve McDonough?

Dr. McDonough: Yeah. I'm not real excited about this. It's probably going to go through but, you know, responding to the current problem by reaffirming a 9-year old report that basically didn't take care of preventing the problem, I just don't know if that's going to be doing that much, if it's going to have much impact. If we're going to go ahead with this, it'd be really nice to have a timeframe for a stronger recommendation this year and we ought to use the interim step just to send something out to the state health departments but – or the public health labs, but I don't know if it's actually doing that much.

Dr. Bocchini: Yeah, I understand the comment, Steve. I think that this is to put the committee on record, but it's not the – the – the work of the subcommittee will continue to come forward with more specific recommendations, guidance, potentially working with Joint Commission and addressing the other things that have been brought forward by Susan, Kellie, the subcommittee and the members of the committee today including yourself. Next, Carol Greene?

Dr. Greene: Thank you and I – I – while I would love to see something stronger just to – to respond to the last comment, I'm not sure based on just simple geography and time of collection that it's like – I – I don't see that it would be possible to get the required samples to be in the lab before 24 hours of collection to have critical results before five days of life. Sometimes it'll

be four, but you can't really mandate that or – and time for all results within five days, so it's possible there could be some tweaking but I don't anticipate that it – it could be anything stronger and I do think that affirming something that was carefully thought out and still after being vetted by the subcommittee seems to be good, I think the landscape has seriously changed and I think a lot of people didn't pay – I think many people probably didn't pay much attention to that report because it came out of a professional organization and yes it was funded by HRSA and it was very collaborative and interactive. A lot of people bought in, but I don't think it has the backing of something like this committee and I think if we have something good out there and this – this committee and then the – the secretary affirms it, I think that changes the standing of what seems to be a – a very good recommendation and I do think that probably the discrepancy is probably that the final recommendations or what people agreed on was achievable and that you put in the final recommendations of the document and then in the body, you might have something a little stronger that you'd say well, you know, in – in – in a – in a perfect world we would do this, but we can't put it in the recommendations because it's not necessarily always achievable. So I think that's probably the force of the discrepancy. But I think it would make – I think it could mean a lot for this – this Discretionary Committee to affirm a report that was – that had a lot of buy-in.

Dr. Bocchini: Thank you, Carol. If there are no additional comments, we will go ahead with the – with the plan and again I want to thank everybody for promptly addressing this issue as it became apparent that – that we need to improve the safety of the system by meeting the standards that – that would best serve the – the children who are screened and their families. So thank you. Let's now go ahead and turn the meeting over to the next presentation. Dr. Alex Kemper, who is the chair of the Condition Review Workgroup is going to give us an update on – from the Commission Review Team on mucopolysaccharidosis type 1 MPS-1. Dr. Kemper leads the Condition Review Workgroup and is a general pediatrician and director of the Program on Health Service Research at Duke University. His research focuses on the implementation and evaluation of screening programs for children, including newborn screening, screening for visual impairment and screening for lead poisoning. Dr. Kemper is also associate editor for Pediatrics, the official journal of the American Academy of Pediatrics. So Alex, thank you. I'll turn it over to you.

Dr. Kemper: Thank you very much. I'm delighted to be able to provide this brief update about MPS-1. Given the time, I'm going to make it a little of a briefer update as a matter of fact, so I'm going to go through where we are at a high level. Of course, I'm happy to answer any more specific granular questions that individuals might have and of course I'd like to leave time at the end of the presentation to get any feedback from Advisory Committee members about specific directions that they might like to see things go.

So if I could have the next slide, please? So I want to just acknowledge all the great members of our consumers we work with. I'm certainly lucky to work with such great people and I'd also like to specifically point out that Drs. Botkin and McDonough are serving as the liaison to the Advisory Committee for this process and I – I appreciate their attendance on calls and advice about how to summarize fairly complex material, and so I think – so first let me remind everyone a little bit about MPS-1. It's an autosomal recessive lysosomal storage disorder caused by deficiency of specific enzymes, alpha L-iduronidase deficiency, and so it's caused by the IDUA enzyme. It's a progressive, multi-system disorder and those conditions we evaluate – it's variable in its clinical symptoms and there's a real continuum of disease severity. There are different ways of dividing the severity, but the – the two frameworks that we use are dividing things between severe and attenuated MPS-1 and the severe group is certainly in the center on this with Hurler syndrome and the attenuated version – the attenuated form includes Hurler-Scheie syndrome and Scheie syndrome. But as I go through the slides, one of the things that I want to focus on is that these are really heterogeneous and overlapping conditions and so I don't want to imply, for example, that Hurler-Scheie syndrome is less significant in terms of impact than – than Hurler syndrome necessarily. Next slide, please. So this – this is just an overview of what we know about MPS-1 epidemiology based on clinical detection. I've summarized by some different continents here and in the interests of time, what I want you to remember is that the overall ethnicity is about 1 case per 100,000 and in general based on the epidemiology of the – that's being reported, the severe form of the – the Hurler's form is the predominant type. But again, these – these kinds of clinical epidemiologic studies are always at risk of bias including under ascertainment, especially of the more mild or the attenuated form. Another thing to – to – to keep in the back of your head is that there are some subgroups that have a higher incidence. For example, there's a – the traveler population in Ireland have a higher incidence. So – someone just go ahead to the next slide. What I'd like to do here again is to discuss a little bit about the disease spectrum. The left-hand column describes Hurler's and then the right two columns review attenuated – the two attenuated forms, Hurler-Scheie and Scheie. So Hurler syndrome, the onset is usually by one year of age and it's rapidly progressive and of course with the attenuated forms comes on later. Again, in the interests of time one of the things I'd like to highlight is just the last row related to the – to the life expectancies where death without treatment in Hurler syndrome is typically under 10 years of age. With Hurler-Scheie it can be in the teens or 20's and with Scheie syndrome could be later in life with a normal lifespan. Again, I – I – I want to emphasize though that these are heterogeneous on a grouping and certainly the individuals affected with Hurler-Scheie can have a – a – a shorter life expectancy just in general being affected with higher morbidity and mortality. Next slide, please. So this summarizes what we know

about life course of individuals affected by MPS-1 based on the MPS-1 registry. So a couple of things that I want to highlight on here. First of all, if you look at the distribution in the registry, you'll see that 57% Hurler, about 24% Hurler-Scheie and 11% Scheie. So if you add that up, that's less than 100% and that's because in the registry not every individual had a disease classification associated with them and the – the reason I'm pointing this out is because of the nature of registries and how people end up getting in it, that doesn't necessarily give you a good sense of what the overall distribution of the condition is. But what I think is really helpful from the registry so you can see the – the age of onset, the diagnosis, when treatment is typically initiated and also the median age of – of onset. Under Scheie, you'll see that we have death listed as 29 so it says only four of the individuals with Scheie disease died. So that's probably less reliable there. So the key things are for Hurler syndrome, the age of onset and the age began on the registry is around six months of age with treatment initiation for those individuals happening somewhere right from 1 ½ years of age and that for those in the registry with the Hurler-Scheie form, the median age of onset was around 1.9 years. Of course, they're both very widespread and treatment initiation for those individuals who – who reported to begin treatment was the less than 9 years of age. Again, I'm going to put the same caveat on registry data in that, you know, it all – all depends upon who goes in there and it's – it's likely to be more reflected certainly the more severe cases because of the [inaudible] naturally end up in these kinds of registries. Next slide, please. So newborn screening is based on the detection of low IDUA enzyme activity. It can be detected in dry blood spots and as with [unintelligible] there are several different screening methods that can be used to measure IDUA enzyme activity, including tandem mass spec, fluorometry by digital microfluidics, and fluorometry on microtiter plates. Next slide, please. So establishing the MPS-1 diagnosis is primarily based on enzyme activity assays. It can be measured in any of the following places: leukocytes or skin fibroblasts, but really you just need to demonstrate it in one place. You don't necessarily need to get fibroblasts. If your IDUA enzyme activity is less than 1% of normal that's considered to establish the MPS-1 diagnosis. However, there are other things that can be supported in terms of establishing the diagnosis, the – one of the primary things achieved with measuring of glycosaminoglycans in the urine. One of the challenges is that in general IDUA activity does not predict the disease form or the severity. Genotyping can help if it reveals a known mutation and I'm going to be talking about this again in a little bit, but this is still a – an – an area of – we're trying to figure out what the – the genotype-phenotype relationships are. Next slide, please. Well, there it is. So there are more than 100 known MPS-1 specific IDUA mutations. The – the challenge of – of – sort of with that is that there are many mutations that are unique to specific individuals which of course makes predicting genotype-phenotype relation harder. There's also a known IDU – IDUA-

pseudodeficiency mutation, again because that pseudodeficiency on [unintelligible] revisit exactly what that means unless people want to talk about that further. All right. Go ahead to the next slide. I'd like to talk a little bit about the treatment strategies, and – and I've grouped them into three categories. The first is hematopoietic stem cell transplantation and the advantage of stem cell transplantation is that it allows individuals to produce their own endogeneous enzyme. It's recommended – the recommended treatment for MPS-1 and there are consensus of treatment guidelines that – that have been produced and they recommended treatment again but then about which – which consensus document you look at, if – if you're going to get a transplant then it should be given before age 2 or 2 ½ years. Otherwise, too much damage has already occurred and also should be reserved for those with normal to moderate cognition. Now the key thing to remember about the – the differences between stem cell transplant and enzyme replacement therapy that I'm going to be talking about in a second is that the enzyme replacement does not cross the blood brain barrier. So for individuals who have got a very severe form, it's – it's a way to ensure that the enzyme gets around the – the central nervous system. So the – the second treatment strategy is hematopoietic stem cell transplant with enzyme replacement therapy. So it's been proposed and – and it's been reported in some small studies that the bridge around the time of the transplant, so while you're waiting for the individual to be able to produce their own endogeneous enzyme as a way to sort of bridge that therapy and it can also augment enzyme activity after stem cell transplantation. There are, for example, case reports of individuals whose stem cell transplant was not effective and they were given enzyme replacement therapy until they were able to be re-transplanted. And then with the – oh, I should mention too while we're talking about enzyme replacement therapy, there is – there is some studies that have been proposed where enzyme replacement therapy is given intrathecal. Intrathecal is a way to overcome the fact that it does not cross the blood brain barrier. I don't have any data on that treatment and so will not be discussing that further. And then finally there's enzyme replacement therapy alone. Again, I talked about the issues with the blood brain barrier, but there's some thought that it may benefit patients with all forms of this disease, but it's generally used for those with the attenuated form of the condition. Next slide, please. Thank you. So the – the goal of our condition review was to evaluate it relative to usual diagnostic and treatment practices. What's the net impact of newborn screening or – or early detection in the absence of newborn screening of MPS-1 on patients' disease course and prognosis, things like age of diagnosis, treatment initiation and outcome and prognosis and survival, to evaluate population health outcomes, incidence and prevalence of MPS-1, and then of course to evaluate the public health system impact. I'll be talking a little bit later about the public health system impact, but I'm grateful to the hard work of the APHL which is really overseeing that component. Next slide, please.

So, you know, we're – we're using our – the methods that you all have seen before where we're conducting systematic evidence reviews to understand screening and treatment effects, physician analysis to understand population of all health outcomes and that section is being coordinated by Lisa Proctor at the University of Michigan, and then the third component is public health system impact, assessing the feasibility and readiness of public health systems to expand screening and follow up, so those, you know, the whole package for MPS-1. Next slide, please. As is our typical approach, we held a technical expert panel teleconference in September 2013 to help us better understand MPS-1 and in the interests of time I won't go through all the individuals and their expertise other than to ask you to read their names and we are grateful for them helping us to get this going and certainly we're going to be recontacting them a we look for unpublished data. Next slide? So this is our PRISMA search flow diagram. PRISMA is the standard way to report systematic evidence reviews. I won't go through the details of the search strategy, but one of the things I'd like to point out is that there really are a lot more published studies related to MPS-1 than – than some of the other conditions that we looked at. You'll see that we're down to 194 individual publications. That number may change because of issues related to overlapping case reports and sort of fine tuning whether or not something really meets the inclusion criteria. But it's going to be pretty close to that number. Next slide, please. I also would point out that MPS-1 newborn screening has begun or at least the planning phase has begun, so both New Jersey and New Mexico are – are planning for it. About three years ago, Illinois evaluated digital microfluidics for screening for MPS-1 and they're now in a preliminary stage of implementation. They plan to use MS/MS with a population pilot to be conducted starting this year and then Missouri as many of you know has begun full population pilot testing that began January 15 of the last year. I'll be presenting some of their numbers. They are screening all newborns and they have [unintelligible] from those individuals that test positive. It's considered to be a pilot, though, because of two – two main reasons. One is they're still fine tuning what the threshold is for a positive screen and because they're still doing that kind of work, it's not being reported along with all the other things on their newborn screening test. So that's – that's really the – the thing that makes it a pilot study. Next slide, please? So this is just a cartoon that – that – that shows the newborn screening algorithm used in Missouri. So they begin with assaying using digital microfluidics such as a fluorometric method for IDUA activity. There is internal laboratory cutoffs that would prompt a repeat test on the same dried blood spot and if that continues to be low, then the individual is sent for diagnostic referral which includes measurements of IDUA either in leukocytes or fibroblasts, measurement of glycosaminoglycans and genotyping. Again, all that's done in the referral centers. Next slide, please. So again I'm grateful to Missouri and I'm – I'm going to specifically thank [unintelligible] Rogers and Patrick

Hawkins for being gracious enough to share with us their data thus far. They've screened approximately 84,000 individuals. Of those 84,000, 42 have been positive. That included one affected with MPS-1 which was confirmed to be the severe form of Hurler's, two that were associated with low IDUA activity and some genotypes of unknown significance, one carrier, five cases of pseudodeficiency, 16 false positives and 17 pending confirmation. So I – on this slide, I purposely did not record things like sensitivity respective to your positive or negative predictive value and the reason for that is again they're still fine tuning what the correct cut off is for false positives and that – that may affect things, for example, like the number of carriers or cases of pseudodeficiency that are identified and also because there are 17 cases that are still undergoing confirmation. It just didn't seem like, you know, now was the time to report the specific test characteristics. Next slide, please. In – in terms of published studies related to newborn screening, there's – there's – there's three things I want to point out. One is a study that was conducted in Washington State by Dr. Ron Scott and two population-based pilot newborn screening studies, one done in Italy and the other one done in Taiwan. Now I – I want to point out that the – in the studies anonymous dry blood spots they found the clinical correlation was not the same as – as conducting a pilot study and a, you know, very cognizant of that, but I think that two of those numbers can be helpful. So next slide, please. Thank you. So I have in the – the first column the ongoing newborn screening pilot study in Missouri. The same was conducted in the University of Washington, the time when newborn screening pilot and the one conducted in – in Italy. The – again, if you think about just a – some genotyping and – well, and some activity which is what the University of Washington study can provide, the – the – their prevalence is confirmed MPS-1 is about 1 in 35,700, from Taiwan it was about 1 in 18,000 and in the Italy newborn screening pilot study test, there were no cases that were detected. Again Missouri, I mentioned before, has identified one case so far but there's these two cases of genotype of unknown significance which are still being evaluated as well as – as other cases that are still in the process. So I don't want to focus on that and again, you will see [unintelligible] quotes around the number of cases that were identified in Washington is because we – there's no clinical correlation. Next slide, please. So just a summary of what we know about newborn screening. IDUA activity can be measured. The screening algorithm is still being refined to balance case detection versus issues like false positives and pseudodeficiency, but challenges exist in predicting the – the form of MPS-1 or – or the attendant severity. All right. Take a deep breath and we'll go to the next slide, which is treatment and our question here is wanting to know what the benefits and harms that are associated with the treatment of MPS-1 and whether or not early detection proves the outcome of treatment and you will see in the following slides that I've broken things up by the severe form and those are the individuals that would be typically treated with hematopoietic stem

cell transplantation versus the attenuated form where individuals would just receive – receive enzyme replacement therapy. Next slide, please. So again, in – in – for this purpose of the presentation, I'm summarizing many slides but – but – but I think we can say that hematopoietic stem cell transplanting compared to the historical controls can lead to increased survival of less than 5% versus 65% at 10 years and it's important also to remember that if you – if – if any individual is going to receive a stem cell transplant, much of that mortality occurs within the first year post-transplant probably as a related to the risk of getting a stem cell transplant in the first place. There can be some preserved development and improvement in mobility. There's little evidence regarding the – the benefits or the harms of transplantation in asymptomatic infants. It does appear that early treatment is likely better, but the ideal timing is unclear. As I mentioned before, what we know in terms of the – the upper limit is that expert panels have recommended that if – that individuals receive transplantation before 2 or 2 ½ years of age and there's little evidence regarding the benefit of combining hematopoietic stem cell transplant with enzyme replacement therapy as a matter of protocol. Next slide? Now I'm going to summarize what we know about treatment for the attenuated form. Enzyme replacement therapy leads to improved outcomes and this is – this is really the highest level of evidence we have because it's based on the randomized trials with onset and follow up. It could include the six-minute walk test and improved scores on the disability index. The benefit of enzyme replacement therapy in – in asymptomatic cases of attenuated MPS-1 is unclear. We simply don't know if you treat those individuals whether or not it leads to a better outcome or, you know, at what point one should really begin treating. Again, this is not completely unlike the conversations we had around [unintelligible] disease. In terms of harms in treatment, enzyme replacement therapy requires chronic infusions and there's the risk of antibody development. So now we're back to kind of process issues. Our next steps are to complete the systematic evidence review. We've identified specialists who we want to talk to help us complete our picture and, you know, this is – this is all a process that you should be familiar with. We have now gathered physician data to think about modeling to understand the projected population benefit in terms of – you have your cases that might be expected to be detected through screening and what the distribution of that might be and I'm going to be talking a little bit, but APHL is working on the public health system impact and then of course we'll finalize the condition review and – and present it to you all for good. So again, our next steps are to complete our expert interviews. We're going to have a follow up with our technical expert panel. We – based on that, our outlining – what we know about how to implement MPS-1 newborn screening procedures which might help with the public health impact assessment and just finalizing the report here. Oops, I'm sorry. I forgot to say next slide.

Male: Yeah, that's [inaudible].

Dr. Kemper: Okay. Okay. And one more time. It's a problem when you have two computers going. I apologize to everyone for that. I'm trying to get through in time for us to have a conversation as well. We have begun to think about the decision analysis to project the public health impact on the population, things we can do there. Again, as I mentioned, just thinking about the number of – of newborns expected to screen positive and ultimately being diagnosed with MPS-1 stratified by form and severity versus the – the degree in which we're uncertain about what that form is going to be and compare that to what we know about clinical case detection. In the interests of time, we're going to go to the next slide which is the public health system impact assessments. Again, this is work that's being conducted by APHL processing [unintelligible] developing and administrating a webpage survey to understand feasibility and readiness and that's going to be distributed to all states in the union including the District of Columbia, and then APHL is planning to conduct a follow up in-depth interview with select state newborn screening programs that – that are representative samples that really do a – do a deep dive and then their plan is to summarize the newborn screening feasibility readiness data and to have that done in – at the same time as our whole systematic evidence review is completed to allow the advisory committee to make a recommendation. Next slide, please. So with that, what I'd like to do is – is stop and – and return the – return things to Dr. Bocchini to find out what questions you might have, including if there are any specific areas that you would like us to focus on as we do our work. So – so thank you for your attention and I hope I didn't [inaudible] too fast to go through that.

Dr. Bocchini: Alex, thank you very much. I think that was a very clear presentation and I know that you – you condensed things for us so that we could complete this in a timely fashion, so we appreciate that. It's very clear that a significant amount of work has already been done for the evidence review. Let's open this for questions from the committee members and/or comments or some guidance for Alex based on what you've seen today.

Dr. Kemper: This is the danger of talking really fast right before lunch.

Dr. Bocchini: Um-hum. Steve McDonough.

Dr. McDonough: Thanks. Just a wonderful presentation as you always do. The question I have is would we be better off giving just a little time to get Missouri's – more information from them to come up with a good recommendation?

Dr. Kemper: Well, I – you know, certainly more information is always better and I think that we – they – they've been very forthcoming in terms of sharing their experience. I – I do think that that would be helpful, but in terms of the timing of – of the decision and – and the level of certainty or

uncertainty that you are all willing to take is – is an advisory committee issue, so I'll defer that to Joe.

Dr. Bocchini: Yeah, I think that certainly would be part of the – the discussion when – when we reach that point as to whether there is enough data on performance and – and – and identification to be able to make a decision, so that – that – that will be an important component as – as it is for each decision made about a condition. Charlie Homer.

Dr. Homer: Thank you. Alex, again, a terrific presentation. I wonder if you could comment a little on this issue with the advantage of early treatment. It looked like there was a significant lag time between onset of symptoms and time of diagnosis and an initiation of treatment. Is there any – clearly not randomized trials there, but is there any hint from any of that data? Is that something you could model as you go forward?

Dr. Kemper: Well I think, you know, so first of all thank you for your kind comment. You know, in terms of modeling, we can only model what we have – there is some evidence about. There are, you know, very small case series that suggest early identification and treatment is better. The experts that we spoke to back when we had the technical arts working on probably felt very strongly that – that early identification was going to be important even if it didn't lead to earlier stem cell transplantation but maybe use of enzyme replacement therapy while things were being sorted out and minimized, some of the musculoskeletal effects associated with MPS-1. But I – I, you know, this is always the trap of newborn screening in the, you know, when you start screening to identify those individuals who tried to know what the benefit of early treatment is. I do plan to follow up with those experts and also very closely with Missouri to understand what the benefits of early identification are.

Dr. Bocchini: Melissa Parisi?

Dr. Parisi: Hi. Thanks, Alex, for a really nice presentation. I was wondering, you know, the dilemma of trying to predict the severity or phenotype on the basis of the early identification by newborn screening is one we've seen before. Is there any correlation with residual enzyme activity with regard to whether they're more likely to have, you know, more severe phenotype based on reduced enzyme activity and then sort of as a corollary to that, I know that there can be changes seen on MRI scan in MPS-1. Do any of the protocols that sort of follow these children longitudinally incorporate that and/or is it an early enough marker that might predict CNS involvement and the need for sooner transplantation?

Dr. Kemper: Those are – those are both excellent, excellent questions. So I – I do note that the – that neuroimaging, I'm going to take your – your questions in reverse order, that neuroimaging is – is kind of part of the evaluation when

these children are detected and, you know, when – when we think intellectually that – that it would help you figure out when to begin therapy or even to decide who has the more severe or the attenuated form because obviously if you have a – a newborn, you know, cognitive testing is not going to be, you know, that – that particularly helpful, so, you know, that's a question that we need to find out from the – the experts is, you know, it's not in the published literature that we've identified in terms of using neuroimaging to predict when individuals ought to get treated. The issue about the residual enzyme activity is – is I think really key. So, you know, what I can tell is if you have, you know, near absent enzyme activity, then – then you're going to have the severe form, at least that's – that's, you know, what – what the experts had told me. But then there's this, you know, larger gray zone where you have abnormal enzyme activity where they're not able to predict the form. I really am hoping that – that some of the ongoing work that's not been published yet is going to help sort that out and I also know – you – you didn't ask about this in specific, but I'm going to take the [unintelligible] to – to bring it up that – that there are teams of researchers that are going back and genotyping known cases of MPS-1 and so although right now we don't have the ability to – to use phenotypes to predict the – the severity or onset of the condition, that's something that – that – that might change. Again, I don't want to speak about evidence that doesn't exist yet, so maybe I'm – I'm smoothing a little bit outside of my comfort zone but, you know, these three issues of residual enzyme activity, neuroimaging and genotyping I think are going to be the keys to sorting out prediction of when – when treatment is going to occur. Did – did that answer your question, Dr. Parisi?

Dr. Parisi: Oh, absolutely. Thank you.

Dr. Kemper: Thank you.

Dr. Bocchini: Thank you. Next I have Fred Lorey and then Dieter Matern.

Dr. Lorey: Hi, Alex. Great job as usual.

Dr. Kemper: Thank you.

Dr. Lorey: [unintelligible] probably [unintelligible]. Will we have access to these slides to go over them [unintelligible] they'd be posted?

Dr. Kemper: What was your question? Will the slides be posted? Yes.

Dr. Lorey: Yes.

Dr. Kemper: Yes, they'll be posted and as a matter of fact, I can email them to – to you once I'm, you know, out of this [unintelligible] access.

Dr. Lorey: Okay, great. Thank you.

Dr. Bocchini: Thank you, Fred. Now Dieter Matern.

Dr. Matern: Yes. This is Dieter. Great work as always. The study that we've been doing where MPS-1 is included and shows similar results when it comes to the performance of the assays. We tested three different assays and what – what strikes me as a significant difference though to the published data and the data from Missouri is the number of cases identified. In our study, it's about 1 in 4,000 who have a genotype that we cannot designate as pseudodeficient and I – we're trying to figure out now whether we got these cases, whether they belong to a specific ethnic group in California or what the deal is – is here. But I just wanted to bring that up, that the incidence of MPS-1 may be very underestimated right now. I don't know what kind of phenotypes these cases have because most of them are variants of uncertain significance and of course we cannot go and follow them up since we don't know who they are. So I just wanted to bring that up.

Dr. Kemper: Okay. And of course, we'll be following a few up with a – our separate interviews we did before.

Dr. Bocchini: Thank you. Now I have Carol Greene.

Dr. Greene: Thank you very much and again, great presentation. I have some information that I think can be helpful with respect to the – some of the clinical questions. So would like to reinforce what was said already about problems with genotype-phenotype and I appreciate what Dr. Kemper had said about, you know, ongoing research, but since some of the – so many of these are private mutations, Dr. Matern just pointed out variants of uncertain significance and I think that the – the – the pseudodeficiency genotype can be incredibly helpful. But both for percent enzyme activity and for genotype, there are going to be lots of patients for whom we cannot predict severity. With that said and I'm no expert compared to the folks who were on your panel, but I do see – see patients with this disorder and unlike some of the other lysosomal storage disorders for Hurler syndrome there are significant findings on physical examination and on a routine X-ray and I am not aware – this is true for Hurler's but not other lysosomal storage disorders, but I am not aware that we would ever see neurologic problems in Hurler's before there are findings on physical examination. So that's one thing that can be very helpful in following up newborn screening. If you know what you're looking for, it – it's there to be seen. The other point I would make responsive to the question of – of course we'd like to have evidence double blind controlled studies about does earlier intervention make a difference and the problem with historical controls of course is that our cardiologists are better, our orthopedists are better, we have all sorts of other ways to try to help people be healthier,

but I think an important point for the MPS is the course of the disorder causes progressive deformation of joints, progressive heart problems, progressive problems with breathing and all of the symptoms of the disease then cause secondary problems and so it's very clear that if you can intervene before somebody has obstructive airway problems, then they don't get heart problems and once you have the heart problems, they don't disappear. Once you have joint problems, once the joints are out of alignment and the cartilage is damaged, even if you make the joints better the arthritis progresses because of the abnormal joint anatomy now. So there is a physiologic reason why earlier treatment is better.

Dr. Kemper: I – Dr. Greene, I – I – I have heard your comments and I appreciate them. One thing I just received a message from Dr. Shannon and I'd like to clarify the record a little bit. Although we have reports that say that New Jersey is planning to add MPS-1 to newborn screening their law right now does not mandate that and then right now they're focusing on Crab A, Pomp A, Gosh A and Pneumopick and Faber A but once – once that's up and running, New Jersey will consider whether or not to add MPS-1. So – so again, just to clarify, New Jersey is not planning to add MPS-1 currently.

Dr. Bocchini: Thank you. This is the value of online communication. Fred Lorey, next.

Dr. Lorey: Yes. This is a question for Dieter. Dieter, were you – were you able to get the information you wanted on [unintelligible] from the California specimens or you still need help with that?

Dr. Matern: No, I got that information and we're . . .

Dr. Lorey: Okay.

Dr. Matern: . . . got approval from the IRB to – to look at the data in that way and so we – we are doing this right now.

Dr. Lorey: Okay. Great.

Dr. Bocchini: All right. Thank you. Jeff Botkin is next.

Dr. Botkin: Yeah, thanks and thanks to Alex for the presentation. I'm looking at the Missouri newborn screening pilot information and I don't know if folks may remember that there were 42 positive first screens and I just wanted to clarify whether that was – what constitutes the first screen. Does that mean analysis of the first blood spot or does – because I think your protocol indicated that it's usually a retesting of the original sample that's part of that analysis and so . . .

Dr. Kemper: Yeah. So let me – let me clarify. So there's a – there's an in-house positive threshold that leads to retesting and then if it's persistently below

the threshold that they've sent then that's reported as a positive, and so these 42 positives that I list are – are not just the – the in-house, you know, first threshold, but these are the ones that have been considered to be positive and – and these are the babies that have gone on to have some sort of diagnostic follow up.

Dr. Botkin: Okay. Yeah, that's exactly what I was looking for. So these are folks who have had the diagnostic workup and 17 pending status confirmation – I don't know whether you've had any additional follow up since the – this data was first acquired, but that seems like a high number to be left in an uncertain stage. Do you know what the etiology is of the uncertainty around that process?

Dr. Kemper: No. I – so these are numbers that – that Missouri shared with us just right before the – the holidays and so I – I can't provide you any more information. There are – you know, I can't remember what the number is, but like four or five centers that – that evaluate these individuals and, you know, I – you know, I can't comment on how long it takes to do their part of the evaluation.

Dr. Botkin: Okay. Thank you.

Dr. Bocchini: Next is Cate Walsh Vockley.

Ms. Vockley: Yeah. Sort of a follow up to what Jeff was mentioning from a genetic counseling perspective. You mentioned the – the laboratory potential for errors and I know APHL is doing the feasibility part of things, but do you have any plans to talk to any of the people in the Missouri program about the experiences of these people, these 42 folks that are going through this what sounds like a relatively extensive work-up and get some more insight into the potential repercussions of instituting newborn screening for MPS-1?

Dr. Kemper: So you – you raise a number of like really important questions. So first of all, I – I can't – at the risk of sounding like a broken record, we – we've talked to the Missouri folk a lot and they've been very, very forthcoming. So I – I just want to publicly thank them again. I feel like I talk to them so much, I should probably just like buy a house in Missouri. But – and, you know, the – the problem is you – you bring up the issues of understanding both the – the benefits and the harms of screening and it's hard for us to systematically evaluate what the – what the downstream harms are from those families because we won't be able to, you know, talk to those individuals directly. I mean, we could get, you know, the anecdotal thoughts of people in the health department, but unless, you know, something's, you know, as – as, you know, well thought out, we just plan on collecting those data. We're limited to – to what we can say about the – the harms of false positive.

Ms. Vockley: I do think that some of the clinicians, genetic counselors in particular, are doing a – a fairly systematic review of that and there may be a publication coming out.

Dr. Kemper: Oh. Well, we'll talk to you.

Ms. Vockley: I can – I can give you a name, Alex.

Dr. Kemper: All right. That's what I want.

Ms. Vockley: Okay. I'll – I'll send it to you.

Dr. Kemper: Thank you so much.

Dr. Bocchini: All right. I have no other questions or comments, so once again, Alex, thank you for an excellent presentation and thank the committee members and liaisons for their good discussion and some feedback that Alex can use as he refines the – the process. So that will conclude the morning session. We are just ten minutes over, so that there is plenty of time for you to get lunch or again, you West Coast people a late breakfast, and then we'll see you back at 1:00 p.m. Eastern time for our subcommittee reports so thank you. We'll talk to you in a little less than an hour.

. . . heritable disorders in newborns and children third meeting. As we are in our final session, we are going to hear reports from the three subcommittees. But first before we do that, we need to do roll call. So we'll go ahead and start. Don Bailey?

Dr. Bailey: I am here.

Dr. Bocchini: Thank you. I am here. Jeff Botkin? Carla Cuthbert?

Dr. Cuthbert: I'm here.

Dr. Bocchini: Denise Dougherty? Charlie Homer? And I think Charlie needed to be at other business this afternoon, so he will not be here. Kellie Kelm?

Dr. Kelm: Here.

Dr. Bocchini: Fred Lorey? I think we have Joan Scott for Michael Lu? Steve McDonough?

Dr. McDonough: Here.

Dr. Bocchini: Dieter Matern?

Dr. Matern: Here.

Dr. Bocchini: Melissa Parisi?

Dr. Parisi: Here.

Dr. Bocchini: Alexis Thompson? Cathy Wicklund?

Ms. Wicklund: Here.

Dr. Bocchini: Andrea Williams?

Ms. Williams: Here.

Dr. Bocchini: And Debi Sarkar.

Ms. Sarkar: Here.

Dr. Bocchini: For the organizational representatives, Freddie Chen?

Dr. Chen: Here.

Dr. Bocchini: Beth Tarini? Michael Watson?

Male: I don't think Beth's going to be here this afternoon.

Dr. Bocchini: Michael Watson?

Dr. Watson: I'm here.

Dr. Bocchini: Okay. Mindy Saraco? Kate Taft? Susan Tanksley?

Dr. Tanksley: I'm here.

Dr. Bocchini: Chris Kus?

Dr. Kus: Here.

Dr. Bocchini: Adam Kanis?

Dr. Kanis: Here.

Dr. Bocchini: Natasha Bonhomme?

Ms. Bonhomme: Here.

Dr. Bocchini: Ed McCabe?

Dr. McCabe: I'm here.

Dr. Bocchini: Cate Walsh Vockley?

Ms. Vockley: Here.

Dr. Bocchini: And Carol Greene?

Dr. Greene: Here.

Dr. Bocchini: All right. Let's go back and see whether we have Jeff Botkin?

Dr. Botkin: I'm here.

Dr. Bocchini: Okay. Charlie – no, sorry. Denise Dougherty?

Ms. Dougherty: Here.

Dr. Bocchini: Okay. And Fred Lorey? And Alexis Thompson. Okay.

Ms. Saraco: Hi, guys. This is Mindy Saraco. I'm here.

Dr. Bocchini: All right. Thank you, Mindy. All right. All right. We are now ready for the subcommittee reports. The first of those will be given by Don Bailey, committee member, who is the chair of the Education and Training Subcommittee. Don?

Dr. Bailey: Great. Thank you. Are my slides there somewhere?

Dr. Bocchini: We need to see if we can get Dr. Bailey's slides up.

Dr. Thompson: Dr. Bocchini, this is Alexis Thompson. I apologize. I was waiting to get into the conference call.

Dr. Bocchini: All right. Thank you. Appreciate it. All right. Do we have someone working on the slides?

Female: Yes.

Dr. Bocchini: All right. Looks good.

Dr. Bailey: Great. Thank you.

Dr. Bocchini: All right. Thank you, Don. Go right ahead.

Dr. Bailey: Great. You can – so I'm Don Bailey and Beth Tarini, who is from the American Academy of Pediatrics, is co-chair of the Education and Training Committee. I don't believe Beth is able to join us this afternoon, but she helped me in preparing these slides and in co-chairing the meeting yesterday. So if you could either turn over control to the slides to me or advance it to the next slide, that would be great. So yesterday, we really did two things . We usually have about a half hour period where we have introductions and two-minute updates from committee members. I don't think there's anything particular to report from that, but we had obviously lots going on in – in the field and lots of excitement around a variety of

different initiatives. As you recall, we are looking at three case studies of conditions that might not be ready for prime time for newborn screening but could be benefit from earlier identification and I'll come back and talk about the whole process we've done with that so far. But we did have a great presentation from Dr. Susan Hahn at the University of Washington on Wilson's disease as used in considerations for childhood screening, and then we concluded our meeting with about a half hour discussion of the nomination guidance and where we are, what materials are available and next steps with regard to that. So – so going back to the early childhood condition analysis, if you recall we've had, you know, presentations about this before, but our committee decided that since we are the secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children, that it would be a useful exercise to think about childhood screening at a time other than the newborn period to see if – and to take some – we were originally going to take one condition and we decided that wasn't really enough examples, so we took three conditions and we've been studying each one of them, getting some input on those six questions. So what is the typical pattern of identification of children with that condition? What problems exist with that current pattern that could be ameliorated to some extent by earlier identification? Would it be even possible to do population screening outside the newborn period? Would it be feasible or desirable? If we didn't do population screening, what would be the likely best case scenario for earlier identification if we could do other things to promote earlier identification? What's probably the best case scenario? And to get to that best case scenario, what level of effort would be required? Would it be for anything ranging from easy, minimal all the way up to a heroic level of effort? And who are the key people that would need to be engaged in any discussions about altering current practice? I just wanted to show you what we've done so far. So we took three conditions. Fragile X syndrome was the first one we discussed, then long QT syndrome – I – I led the presentation and discussion of Fragile X. Beth led the presentation and discussion of long QT and then Dr. Hahn the discussion about Wilson's disease yesterday and so these slides are really just very preliminary slides and I'm not going to go through them, but I just wanted to show you because we really – a lot of this information was generated on the fly while we were discussing these conditions yesterday. But this is an – this is what we will be presenting at our next advisory committee. So we'll take each – there'll be a prior slide potentially describing each condition. What is it? How common is it? And what are the consequences of it and so forth? And then we'll have slides comparing the patterns of identification for children with that condition, you know, the – the problems that exist, you know, ranging from a diagnostic odyssey in Fragile X and missing early intervention programs. In long QT, the problem there is the first presentation could actually be sudden death and Wilson's disease, for example, liver damage and other serious conditions could occur because of the pattern identification that is

currently happening. Would population screening outside the newborn period be at all feasible or desirable? I think we'll come up – we'll come back and discuss this in more detail in our next meeting. I think, you know, all of the use conditions could be screened at a later period, but the point – the fundamental question is how and when and who would do it and would these be standalone kinds of screenings or would they be folded into some bigger panel that might happen and when would that panel happen? So we don't – we won't have answers to that, but these three conditions are very informative about helping us think through what these considerations might be. In the absence of population screening, what's the best case scenario for early identification? So for example, like again in Fragile X we said, you know, if every pediatrician followed the APA guidelines for screening at 9 and 18 – developmental screening at 9 and 18 months of age, any questionable screening immediately followed by complete evaluation, any child with documented developmental delays then immediately referred for genetic testing. So even if we – if all that was done, then in the absence of population screening there's been more symptom-based screening, is it the best case scenario? It'd probably be 16 to 18 months of diagnosis for the most severely affected males and so we'll do that kind of analysis for each – each of the – each of the other conditions and of course again, the question we'll have to be addressing at some point is do we always just rely on symptom-based screening or testing and try to improve the diagnostic process once symptoms occur or do we do some pre-symptomatic screening and, if so, when would we do that? What effort would be required to change the current paradigm? All of these would take quite a bit of effort to – to change and clearly, you know, pediatricians are key – key to all of these disorders, but many other specialists that would need to be in place as well. So our next steps is – are that over the next – next three or four months, we'll be finalizing these tables and expanding them some, comparing the three conditions. We'll prepare a summary of major issues and themes as it emerged from our – our work and we'll do a final report to the committee in May. We don't really anticipate any formal action items or, you know, recommendations or requests to the – to the secretary for something different. This is more of an exercise for informing the committee to start thinking about things other than newborn screening. Excuse me. The second area just to talk about briefly is, you know, one of our goals has been to provide better guidance for advocacy groups and others regarding the nomination and review process and in order to increase public transparency for what we do and the rationale for decisions made and – but even more importantly, not that the first one's not important, but to support future nominators in preparing successful application packages. So we've done a series of activities. Atlas Research did some interviews and prepared some draft documents for them. We reviewed those last summer. We discussed them in our September meeting and we felt like that we were still missing the voice stakeholders in – in those documents and so Atlas just before their

contract was up conducted interviews with four advocates who had been through the nomination process before. So I am not a qualitative researcher, but I did read those and have pulled out a few themes from those and so I'll just go through some of the major things that came up – came up from those interviews. First and clearly all four nominators expressed great appreciation for the work of the committee and the systematic approach to decision making. They realized that we – that that – our nation needs a rational process for deciding what conditions ought to be included in – in newborn screening and so they're very appreciative of the committee and its work. A second point is that the nomination forming the matrix that we've developed for decision making seems simple if you just look at them on the surface, but behind and there's enormous complexity in work and the big challenge really for everyone is that we have a standard – we have a standard form and a standard process, but in reality there's much individualization that has to occur for each condition because each condition is different in terms of how it presents, in terms of who's by when, the nuances of treatment, lab tests and so forth. So with the general questions that each one needs to be – needs to ask – ask and answer, but there's a very – it's a very much individualized process. These were all again four people who had been through this process and their advice to advocates, other advocates, was that you need to realize how much work that the advocates – advocates and nominators need to do to help advance the cause in addition to public testimony, the most important being to form some sort of steering committee or experts and the stakeholders that works over time to prepare a strong nomination and when gaps are evident in the review – in – in the – in the data that this steering committee would help push forward both a research – push forward a research agenda and a clinical agenda – addenda to fill in the gaps and have a champion who will guide and lead the process. Those were – that was some advice from the advocates to other advocates. There are certainly examples of terms that I know many advocates may not – were not pleasing the committee with, things like analytical validity, then also concepts that advocates and researchers might see differently, for example treatment or benefit and we've heard public comment, just about every time, around – around this – around this question. So clearer definitions of the former types of terms like analytical validity would be important and then robust discussions about other broader areas, like what do we mean by treatment would also be useful. All the interviewees felt that some sort of instructional manual would be useful in preparing not only the nomination form but in – in preparing the kind of a portfolio or a business plan for how – how to address gaps in knowledge and ideally advocates are nominated would have someone of their [unintelligible] to guide them with specific advice on next steps and data needed. That was something that came through pretty clearly in the interviews. Especially needed is advice on whether and when the nominating condition is – is a quote from one of the interviewers is truly ready to be competitive.

Obviously we've talked about this as a committee before, but lack of clarity on sources of funding to do the work needed to provide the evidence required obviously NIH, CDC, MCH, a variety of agencies can and do fund this, but there's not necessarily a single structure or portal to go to to figure all that out and in – in – and in conclusion, although again they – the interviewees very much appreciate the systematic approach that we're taking to review, I think all of them felt that the process takes too long and that – and are – and all are wondering whether we'll be able to sustain this kind of model and conduct reviews with sufficient expediency as the number of nominations likely increase in the – in the future. So where are we now? Well, in terms of what we actually have available for nominators, there are really three things – well, more than three but three core things. One is there is on the website a description of the process and there's a link to the nomination form and the article that Alex Kemper and other members of the committee wrote and published recently on the decision matrix and the decision review process is very helpful, and of course there's a lot of other professional literature that's out there. But the Kemper et al. article is the best and most current discussion of the – of the committee's process. So what – what do we need now? Two things came out of that discussion. One is this idea about our navigator that could respond to questions and help provide guidance for nominators and then hyperlinks on the nomination form to explain terms and provide further details about what is needed. If we could get these two things in place, we think it would help future nominators and applicants considerably. Of course, the big question is who – who will do this and so we will be turning back to the – to HRSA to ask them about the – the Genetic Alliance has told us that in the past they have performed the navigator role and they would be willing to continue to do that if that became part of their agreement with HRSA and so we'll have some discussions and we'd like to encourage – encourage that we think that would be very helpful going forward and – and in addition, we need to figure out who is going to be writing some of this information that would be hyperlinks on the nomination form to explain terms, provide further details. I believe that's it. Yes. So thank you.

Dr. Bocchini: Don, thank you very much. That's a very concise report of all the activities and – and they're both pretty remarkable to hear all of the things that are going on in the different groups of – and organizations that are represented on that subcommittee, so thank you for your work and – and best results. Were there any questions or comments related to Dr. Bailey's presentation? If anybody – committee member has a question or comment, again please use the hands up icon. If there are none, let's go to the organizational representatives. All right. If there are none, then let's go on to the second report. Again, thank you, Don.

Dr. Bailey: Yeah, well, I just want to thank the committee – subcommittee members and also Kathryn McLaughlin and Alaina Harris who provide just

tremendous – from HRSA, just provide tremendous support to our subcommittee, greatly appreciated.

Dr. Bocchini: Thank you, Don. The next subcommittee report is from the Follow-Up and Treatment Subcommittee, Carol Greene, who is chair of that subcommittee, and represents the Society for Inherited and Metabolic Disorders as its organizational representative. So Carol?

Dr. Greene: Thank you very much and I would like also to thank and part of this presentation will be from Chris Kus, who is co-chair and who is been heading one of the projects that we'll report on and who is representative – who is onto the committee from ASTHO and I also want to help – thank Jill for incredible staff work and some enormously active – if I could have the next slides – lots – lots of work from the members of the subcommittee and experts. Basically once you're on this committee, we don't let go of you. You keep working and I really appreciate all the – the hard work and input. So I'd like to start with a – next slide – reminder. We've seen this before. I show it regularly just because it – be sure to remind everybody that the subcommittee works at the request of the committee and this is the – the charge that has been given to the subcommittee to look at implementation, identify barriers, to develop recommendations for overcoming any barriers and to address issues around responsibility for both short and long-term follow up including treatment and the next slide. So the committee as you will recall identified some priority activities for the subcommittee. Priority A, implementation – we have a project near completion Dr. Kus will report on. Priority B, we have no current projects and Priority C I'll report on and the next couple of slides just tell you a little bit about what we're doing. Next slide. So Priority A, you'll hear from Dr. Kus and we had just to remind you that we had initially planned two projects but at the last meeting we had all – the committee had agreed that it would not be useful for the subcommittee to be tracking CCHD implementation. So Priority A project is – is about to be completed. Next slide. Priority C is – the charge from the committee is to explore the extent to which we can tell whether or not we're improving the lives of children after finding affected children by newborn screening and we are working on a case study there that's led us to a – suggesting a framework and the next slide. We have no current specific projects assigned at this time for Priority B, which is the – the closing gap through systems of care and – but we were instructed by the committee to try to consider roles and responsibilities and long-term follow up in – in any of our projects and the next slide. Just to let you know what we've been doing since the last meeting, 2013, we have regular conference calls focusing on those priority areas and the projects. We have been working on the Priority A project, which you're about to hear from Dr. Kus and the Priority C project that I will report on. I believe the next slide turns it over to Dr. Kus. Next – yep, there we go.

Dr. Kus: Okay. This is Chris Kus and I can't see the slides, but I – because I've got some Internet problems, but I'll just describe. What we – what has been in your briefing book and I know Dr. Bocchini sent a note out to folks that we're looking to get acceptance of this document to go forward in terms of publication and dissemination of the information to the field is the paper that's entitled Some Lessons Learned From Early Human Detection and Intervention that may be applicable to corticocongenital heart disease screening.

Dr. Greene: And here's the next slide, please.

Dr. Kus: Thank you. And the lessons – the major lessons that are in the paper are one, that the steady program of newborn blood spot screening program should strive to better coordinate the various components and support child health data innovation efforts. The second point was that the state health department should play a leadership role in implementing electronic data systems that utilize standard base messaging to reduce errors and enhance timeliness in data reporting. The third point is that screening programs should require child [unintelligible] date for quality improvement efforts and the fourth point is our appropriate support, federal and state, will be needed to develop, implement and maintain the CCHD screening system and I looked at the – the reference in the briefing book, the last [unintelligible] I – I will correct that. But what we're looking for is acceptance from the committee to go forward in publishing and disseminating this report. So I'll stop here and see if there are any questions or comments.

Dr. Greene: And that's the next slide.

Dr. Bocchini: [unintelligible] Yes, thank you. Now I – you know, my feeling was that since Chris and Carol have brought this to the full committee and the full committee had opportunity to provide input and he has supplied the four major areas that – of – that – that would be the lessons learned that with the impending input that comes from the committee today that this is approved to go forward because I think the committee's already proved that with the changes that were recommended then and then adding on to any changes that would be recommended now, so let's go ahead. I think we wanted to make sure everybody had a chance to review the – the – the – the – the paper draft and make any comments or anything – any considerations related to what you read. So we'll start with – we'll – we'll work through the committee. Any questions or comments? Dieter?

Dr. Matern: Hi. This is Dieter. I just wonder whether the subcommittee considered state rules and regulation laws with respect to data privacy, data retention, including newborn screening results. As you know in Minnesota, newborn screening results are being destroyed. So the only thing that is left is the medical record and as reading the document, I wasn't entirely

clear, you know, whether the – the databases that are mentioned would fall under or would – would have problems to be created given some states interest in laws.

Dr. Kus: To – to answer that, we – we didn't consider the – the state particulars, but we're trying to give general recommendations that could move program for – that we think would be helpful within the considerations of the state.

Dr. Bocchini: Are there additional questions or comments from the committee? If there are none, I – I think that this – this can go forward now as a publication of – of the committee. So I think you can proceed with this – with the blessing of the – of the full committee.

Dr. Kus: Thank you.

Dr. Greene: All right. And thank you very much and the next slide.

Dr. Bocchini: Before you go to the next one, we – we will post the publication on the committee website when it is completed, when – when it's published.

Dr. Kus: Great

Dr. Greene: Thank you for that clarification. Yes, it's some – some places would not publish if it has already been posted, so – and – and of course I think there's HRSA clearance as well.

Dr. Bocchini: Correct.

Dr. Greene: Thank you. So the next slide – just to remind you, we have previously submitted an earlier draft of a report of a process that's turning into a paper that is tentatively titled The Framework for Assessing Outcomes from Newborn Screening. We have multiple new drafts. We're in the process of we're actually – I – I think quite happy that we have a framework and we're very happy to hear from the committee with an early draft that we are on track. We are in the process of rewriting, tightening, considering whether we have too much in there. It might end up being two papers and we're in the process of testing the framework that was designed around the case study of – of hemoglobin – of sickle cell, testing it against PKU and the next slide is our last presentation for the committee. We've had more – some additional iterations, some discussion about the goals – let's see. Specific issues you can see there being considered that we need to be sure are addressed in this framework of issues of privacy, making sure we have the – the family point of view. It – it is a work in progress. We were not asked to provide another draft to the community because it is definitely a moving target. We do hope that we will have a draft to submit to the committee before May that would be a – a – a draft for committee approval and we think we're on track to do that. So the next slide is to briefly report on our meeting yesterday which was lively and incredibly

useful, certainly to me. We had brief updates for old business. There was a brief report on tracking of the integration of newborn screening with other data systems. We had previously expressed some interest and there remains to be some interest in the possibility – there is so much going on with transition in long-term follow up and possible interest that at a future subcommittee meeting we might be interested in hearing from the status of that work and don't know if that would be of interest to the full committee, but – but of interest to the subcommittee, and we spent the last roughly half hour as instructed since we are – we have just completed one project and we are nearing the end of another, looking at our priority areas. We have the following and I – I hope the committee – subcommittee members will agree that's a reasonable summary of our discussion. Some ideas of possible future projects that we would like to hear the committee discuss, there's some pros and cons in each and of course we each have our biases. So one possible project would be to explore the – the roles and responsibilities of the hospitals and birthing centers in newborn [inaudible]. Of course there's a lot of work currently going on in that area, certainly with respect to transport of samples and we've heard from March of Dimes that they're – they're looking more broadly at responsibilities. So that may actually be redundant to ongoing efforts of APHL and I would now add March of Dimes and others, something that could be looked at but possibly redundant. I will be honest and say that very dear to my heart is the second bullet, which we've been working for quite some time to see if in the subcommittee we could identify a – a doable project that would address the models of and access to care and I think based on the discussion we had some idea that this would be a follow up to the – the – the current framework project and also a follow on to a I think very landmark report, the subcommittee and committee has done before about the – defining what is long-term follow up. We could look at the current models that are used by states in particular, look at what are some of the successful ways or successful model for delivery of long-term follow up. I think this would mesh with but not duplicate what we heard described from March of Dimes. We had some ideas of how such a project could look, that it could involve a survey, probably would require convening of a stakeholder meeting, it could be – could be webinar and we would expect that if we work on that there would arise some potentially useful information for states and other stakeholders and some important questions because we expect that we would see variability across states and across solutions that workforce issues and transition issues would come up. So we think it would fit with HRSA's priorities. On – the next bullet is a very much more specific possibility to address the responsibility for newborn screening in out of hospital birth and that could be a – a very much more circumscribed project. They didn't get into any discussion of how that would be done and the last bullet would be that – would be a follow onto the framework product and look at – implement – what are the elements that need to be formally considered when scoring or judging how

a condition added to the newborn screen, how a state could implement that. It's possibly – I wasn't entirely sure. Alex was part of the conversation – Dr. Kemper was part of the conversation. It didn't seem as this would be completely redundant to what the full committee is doing, but it – it – it might be and I would like to open the discussion, you know, turn it back to Dr. Bocchini and see if there is interest from the committee in having the subcommittee explore any one of these or any other projects.

Dr. Bocchini: Thank you, Carol. I – I – I certainly would agree with the first bullet that – that we've learned there's a considerable amount of effort going on, not only within our laboratory committee – subcommittee and other organizations that I don't want to add redundancy, so I think that it would be better to move the committee in – in a different direction so that other things could be looked at at the same time and so with that, let's open this up for discussion of committee members for the other considerations that Carol has raised and on her subcommittee. All right. I see no – no one raising their hands, committee members. Organizational representatives? So I guess the – the lateness of the day and the timing, I think we need to consider this in some more detail, Carol, and then perhaps after some consideration we can give you some feedback from the committee to consider one or more of these other proposed new projects to – to move into. I – I particularly like the idea of looking in more detail at long-term follow up models and – and – and look at outcomes related to specific conditions, but . . .

Dr. Greene: May – may I – may I ask then just in case, if the lack of comment is perhaps – because what you just said, you certainly sound like as the committee chair at least, you favor the one that I favor and that we did have a lot of discussion about. Might it be that the lack of comment was a sense of consensus, that perhaps our second bullet might be a – a way to go and – and perhaps that the subcommittee could consider specific approaches and bring that back to the committee?

Dr. Bocchini: I'm not sure that I could say that that – the silence means consent, but . . .

Dr. Greene: Well, that – what I – what I was mainly proposing is that if you perhaps polled the committee and see if we might have – because we'd like to start planning and we certainly do care about the whole issue of access and – and – and models of delivery and if there could perhaps be a sense from the committee that we should further explore that second bullet, we could – could get to more specific suggestions of how might – we might approach it.

Dr. Bocchini: Okay. Well, why don't – I think in the interests of time and unless committee members wish to respond? I don't see any. My suggestion, Carol, would be to flesh this out a little bit further to a more specific

proposal that the committee could look at, perhaps at the next meeting, and . . .

Dr. Greene: That would be lovely. We will – we will flesh out a – a more specific proposal based largely on that second bullet and it, you know, could overlap with the fourth bullet. But we'll – we'll flesh out a proposal based on that second bullet.

Dr. Bocchini: Yeah. And I think for – with – with more details and – and – and with, you know, more information, I think could have a better idea of where this potentially could lead us and – and – and the – and the value of it.

Dr. Greene: Thank you.

Dr. Bocchini: Okay. Thank you very much. Okay. The next subcommittee report is the balance of the report from the Laboratory Standards and Procedures Subcommittee. Kellie Kelm who is chair and committee member I believe will provide this portion of the report.

Dr. Kelm: Yes, thank you. We don't have – we had one other item that we discussed and so I'll talk briefly about that, but obviously [unintelligible] time runs out. But the timing is from transport issues, so next slide. First here just wanted to gather the priority [unintelligible] standard to your subcommittee. We have Priority A, which is to review enabling and/or destructive technologies and this is what I'll be talking about in the next few slides, which is our succinylacetone implementation survey update. Priority B is to provide guidance for state newborn screening programs in making decisions about lab implementation, integration, follow up and quality assurance. Okay. The second bullet is determining the timeliness – timeliness of specimen transport which we will continue to work on and the first bullet is the [unintelligible] which is a [unintelligible] that would be a skeleton that could be used starting with SKID and then for others after they're added to the panel which would help lots in an implementation, integration, follow up for new conditions as they are added to the rest and this could [unintelligible] back the update from the group working on that. In fact, that should be complete and room for our presentation at our meeting in May and our last Priority C to establish a [unintelligible] review and [unintelligible] of the recommended uniform screening panel. At this time we have no items under Priority C and – and no updates. So moving on to the next slide? Susan and I want to thank our fantastic subcommittee watcher and the participants. We had great participation this time as well as some other voices and – and the people that we made [unintelligible] and – and [unintelligible] and so we appreciate all of the participation and most of our [unintelligible] you can see here and next slide? So we [unintelligible] that we did briefly discuss – discuss in 20 minutes was the succinylacetone implementation project update, so next slide. To remind you all briefly, there was a lot presented

on this at the September meeting both in the subcommittee as well as to the full committee. So I only have a few very short bullets, just to remind you guys. Tyrosine is not a specific marker for tyrosinemia part 1 but it's also over other conditions which makes it not the best marker to detect this disorder. Succinylacetone is a specific marker for – for tyrosinemia type 1 but it is not detectable by routine newborn screening due to the fact that by next spec and some of the issues that I will discuss and it's the – it's the variability in terms of – of commercial [unintelligible] that are today we're in one [unintelligible] that's available and used by [unintelligible]. So we'll move on to the next slide. So let me – I don't have a slide here, but Susan's team worked on reviewing their position two data that they had, looking at not just – at [unintelligible] but also internationally, you know, the labs that participate in the proficiency program and so both [unintelligible] are for the interlinks based on lots of things including what method they used to detect tyrosinemia [unintelligible] succinylacetone and wanting to look at the reform to see how well these markers were and then here is also providing some data from the FOS also looking at the systems that use the different markers and how well they're doing in detecting tyrosinemia type 1. So then [unintelligible] as mandatory to effectively U.S. labs that were using succinylacetone and the [unintelligible] labs using tyrosine, asking questions about why conventional labs weren't using succinylacetone so that we could get our hands around what the barriers were to moving to that [unintelligible] shows a more specific marker for the commission. So here's – you know, so the conclusions from the work that Carla and her group have been doing [unintelligible] and the obstacles that the labs that were still using tyrosine, so what were obstacles to removing succinylacetone and most of the direction operational in nature. So a few states had spoken up and said that they have concerns about the performance of those [unintelligible] that are succinylacetone enough that they don't want to switch from the ones they're using because it doesn't succinylacetone and they don't want to lose the kit that does offer succinylacetone until the performance of the kit changes. The other issue would be at barriers that we could [unintelligible] lack of money, space, staff and equipment. In order to add succinylacetone most of the labs would actually need to add new lab specs in order to do that. There has been some discussion with states that include [unintelligible] has changed and [unintelligible] has been ordered to not do that. That's something we might – that might be [unintelligible] and added to the discussion of the paper and Carla said she's going to continue to work [unintelligible] states to add that to the discussion section to make sure that she does broaden the scope. The next slide? So Carla and her group are – and Dieter are currently working on drafting a publication. The publication will be including the analysis of the CDC, the NSQOP producing data and, you know, minutes of that was presented to us in September as well as the announcement of the article H data that Dieter's been pulling out and then the discussion currently that's

[unintelligible] service around the discussion of the issues that would be the main obstacle in spite of [unintelligible] action in imitation with which she said she's still talking to folks to make sure that she can include all their – their, you know, their concerns in the discussion section of the paper. Next slide? So progress and status of the [unintelligible] is in process and Carla said it should be – the first draft should be complete soon and the plan is to – once it's – it's – the draft is done, we can send it out to the subcommittee members to get input and we can do it before the next meeting. It was originally talked about in September, that is mentioned publishing it in the MMWR, but the feeling is [unintelligible] there is a lot of [unintelligible] is the preference to actually submit it to a peer review journal and I think down the road and of course to, you know, timeline is always dependent on the – the time of getting it to the peer review process, you know, we would like to bring that forward for consideration of the committee and I think the feeling that we got was not that, you know, as if through obstacles to adding [unintelligible] appear to the operational nature and that it would be very informative to [unintelligible] but there is not necessarily any actions and recommendations that we could see the committee taking in order to referred uptake of succinylacetone but that posting of this presentation on the website for the committee would obviously check – put out the rumors about these operational issues and whether or not down the road there would be some work to address those. So I think that's my last slide. Next slide? So I will, you know, update at the next meeting as to where reporting, the publication [unintelligible] by our next meeting. So that's – that was it and there's going to be time for the next – for the subcommittee that's – that's meeting. Thank you.

Dr. Bocchini: Kellie, thank you very much for a very clear presentation. This is now open for questions or comments. I guess one question I had is the – is – is that a true issue, the performance of the succinyl or acetate kits?

Dr. Kelm: Well, the – the – the discussion at the subcommittee where there was input from Dieter as well as others is that although some of these states are obviously [unintelligible] concerned about the performance of this kit, the data that we are seeing is that it is actually not missing babies that are having an issue at screening as – as far as we could tell, so obviously it's just a – in a lab and [unintelligible] make sure that issues that come up why we invalidate them and a follow up and [unintelligible] as we move forward to make sure that those are appropriate. But we – we – that was what we heard was that, you know, those concerns, people didn't see that natural screening – screening performance.

Dr. Bocchini: Okay. Thank you. So this is open for additional questions or comments from the committee and the organizational representatives as well. All right. I have – no one is raising their hands. I – I think this is really a good example of collaboration with the committee, the CDC, experts in

the area and I think this will go a long way to improve the – the evaluation for – for this condition. So I want to thank you all for all your input and make that happen. So we look forward to seeing the publication. Well – so the final topic of the meeting, we did leave a ten-minute period to raise any discussion on possible future meeting topics and obviously we have a number of things going at the moment and – and so just want to see if there is any discussion on – on – on other future meeting topics. So first I'd like to see anything from the committee and then we'll follow that with organizational representatives. All right. Steve McDonough?

Dr. McDonough: I've got a couple ideas. One with all the – I don't know what the right term is, changes that have gone on in Washington with sequesters and budget cuts and shutdowns and all that, how it's impacted what federal agencies are doing and – and research program delivery. I'd be certainly interested in getting an update on how this has all impacted what we're trying to do. I know we're certainly having webinars not face-to-face, one way it's impacted us. The other is when we get together to review the timeliness of newborn screening, we talked about earlier today, I think it's really important that the families who are looking at this will have the opportunity to comment on what we're coming up with, either suggestions on improvement from the 2005-2006 document because I really, really would be interested in hearing their suggestions for how we can do better.

Dr. Bocchini: All right. Thank you. I think there's no question that we want to move that project forward with the – with the subcommittee to – to come to some recommendations and guidance for – to help stage them and work closely with APHL and others to kind of bring that forward as quickly as – as we possibly can so that we can have a positive impact for families, so I certainly think that's a very important area that we need to work on between meetings to – to move that ahead. Carol Greene?

Dr. Greene: Thank you and I just received something today, I just sent it to Dr. Bocchini and I don't know if you have the capability of – of sending around right now, but there is a – a new and I think very important issue that's happening with coverage of genetic – of molecular genetic testing. There've been a lot of troubles that the I think CMS and FDA have been working on, new codes that what's brand new is or at least new to me is TriCare has reviewed the new CPT codes and has decided that they are no longer covering something on the order of 100 different tests that they have covered in the past because to quote, I – I just have this from a – a – a reporter, but the codes allow the agents or allow identification of specific laboratory tests that have not been approved or cleared by the FDA and/or failed to meet TriCare coverage for – criteria for coverage, so they are among other things not covering cystic fibrosis carrier screening for women and I'm sure there are quite a number of other laboratory tests and the assistant secretary of defense apparently has already pointed out that member of the military who receive their care directly from the military

now can get testing that is not available to members of the military who receive their care from private insurance covered by TriCare. So I think we have a bit of – I think – I think we have a major crisis in coverage of genetic testing and I think to have the committee try to understand what's going on and see if there's any potential for guidance to the secretary might be useful. Of course, the decisions are made in the private sector, but the secretary could hopefully provide guidance that – that could be useful.

Dr. Bocchini: Carol, I appreciate that. In fact, the committee has been made aware of this issue and we're exploring where potentially that might be best addressed so that we appreciate your bringing that to the attention of the full committee and we'll – we'll determine how best we might be able to participate in addressing that issue. So thanks. Michael Watson?

Dr. Watson: I was only going to say I am in complete agreement with Carol. There's a – a major mess right now to many providers around the country having to revert back to the – the last best technology of chromosome analysis instead of using [unintelligible] rays and things like that because they're not being covered and it's all an extension of decisions made at CMS initially during the gap fill process around all the new CPT codes for molecular diagnostics, but then got picked up by a lot of Medicaid carriers, you know, the issue of carriers for CF is – is an – a problem only because you can't do any kind of prevention within CMS or Medicare money. That is something that private payers can cover, but CMS is precluded unless Congress actually legislates coverage of screening types of activities like that. But I do think it's a major problem and there's a lot of service being denied now and I think the AMA is beginning to collect examples of lack of access to what are considered standard of care services because of payer decisions made over the last three to four months.

Dr. Bocchini: Mike, do you know of any efforts by other organizations or those organization representatives like AAT and AAFP and others have been involved in – in – in working on – on this issue?

Dr. Watson: I don't know that they've dealt with the issues of molecular diagnostics to any extent, because it really is very much focused on that. There are certainly a number of groups. In fact, we had a meeting with – with Richter, the – the director – acting director of CMS or Medicare about a month and a half ago and out of that got, you know, a letter basically blowing us off because it was, you know, so much of what we deal with isn't something that Medicare sees. It's things that are in a Medicaid population, yet Medicaid is adopting some of the Medicare coverage and pricing policies and, you know, it's an absolute mess of people misunderstanding who's obligated to follow whose policies, but it's forcing preauthorization to an enormous extent out in the clinical community and

many payers now won't even speak to a staff person. They require the physician to speak to them to justify their patient having a test covered and they certainly don't have time for that in our certain current healthcare environment.

Dr. Bocchini: [unintelligible] I agree. Any other comments related to this specific issue? [unintelligible]

Ms. Wicklund: This is Cathy, guys. I'm sorry. I can't use my – for some reason, my hand raising thing doesn't work. I – I just want to echo Mike's comments and this has certainly been an issue in the genetic counseling community as well, especially prenatal, you know, where tests were covered and now those – they're being denied and genetic counselors are spending a lot of their time trying to convince insurers to cover tests that historically have been covered. So I agree.

Dr. Bocchini: Thank you. Further questions, comment? Adam Kanis?

Dr. Kanis: Yes. Hi. I'm the DoD rep, organizational representative and I do want to confirm that it is getting a lot of attention from very high levels, but – and it's in a lot of flux, but there's nothing really that I can say right now more about that.

Dr. Bocchini: Okay. Thank you.

Ms. Wicklund: Dr. Bocchini, this is Cathy again.

Dr. Bocchini: Yes.

Ms. Wicklund: And the only thing – if we're – if people do want to have coverage topics, there are some current things going on with NSGC with regard to coverage of genetic counseling services or genetic counselors as independent providers and that is an update that we could provide as well. I know Cate's on the phone, but that is something that could be tied into that discussion if people are interested in that.

Dr. Bocchini: Okay. Great. We'll – we'll keep that in – in mind and make sure you're aware of – of things as they evolve. Carol Greene?

Dr. Greene: Yeah. And – and I appreciate that the – the folks who have pointed out the issues of coverage for genetic counseling and the larger issue of coverage for genetic tests and it sounds like it's possible that the – the DoD representative, that they may be on their way to – to solve that particular problem, but that – that would be only one instance of a much larger problem that – that Dr. Watson described that is affecting people well beyond TriCare. So I – I think it's a general issue.

Dr. Bocchini: Agreed. Thank you. Other comments or additional topics? All right. Hearing none, this will conclude the third meeting of the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. Want to – a warm thank you to all of the committee members, organizational representatives and the public for attending this webinar. Please be sure to close your Internet browser window so that you are logged off of – out of the webinar at the conclusion of these remarks. So again, thank you very much for all of your contributions and your work to make this committee so successful. So thank you.