Transcript: Afternoon, Part 2 – January 31

Event ID: 2089086

[The event is returning from a lunch recess, and will reconvene shortly.]

I would like to remind you that our lines--your lines are open. And sir, you may continue.

All right, welcome back to the second part of our meeting today. What I am going to do first is go through the reminders. So for committee members and others, sound will be coming through your phone lines. So have your computer speakers turned off. Hold your questions and comments and we are going keep the lines open, as we did this morning, so that we will not have a queue for individuals who wish to question for comment. And please remember to state your name before every comment that you make so that we can have proper recording and identification of individuals who make comments for the transcript and the minutes. And if you have problems with your phone line, press star 0. Members of the public, the sound is going come through our computer speakers. Hold your questions and if you have a question, go to the lower part of your chat box, type in the question and then click the send icon. Remember that following this session at 2:45 eastern time, the subcommittee meetings will start. They will go from 2:45 to 5:00 eastern time, and subcommittees will be listed in the webinar. So I now need to take attendance. Don Bailey.

Present.

I am here. Jeff Botkin. Not yet. Okay. Carla.

I am here.

And Sara is here. Melissa Parisi?

Here.

Thank you. Alan Guttmacher

Here, here.

Thank you, Alan. And Kellie.

Here. Michael Lu

Not yet. Stephen [Inaudible - Low Volume] all right, [Inaudible]

I am here.

Thank you. Catherine Wicklund? Here.

Thank you. Andrea Williams.

Here. Your sound went down a little bit.

Okay. We'll try to make sure that you can hear us. So let's go back now and Jeff, have you made it?

Yes, I am here.

Okay, great, and then um, I guess Stephen.

Yes, I am here.

Okay, great. Okay, so we are now ready to go on. So, on the agenda Alex Kemper is going to give us-- Dr. Kemper is going to give us an update on the Pompe review process.

Operator, can you mute all of the other lines?

Yes, ma'am, I sure will.

Thank you.

So good afternoon. I am delighted--I am really delighted to update you with where we are. And let me first start by thanking members of the work group. I can say with certainty that we have the best darn members on this work group that one would hope for. And I would like to thank you them. So I am going to be talking a lot about the system gnat I can review piece. And [Inaudible] is going to be talking about the public health impact. I would like to look at two other things, I think you know, I am from Duke University. However, we do not overlap in this domain at all. I would also like to thank two people who are not on the list. Williams and Homer who helped us to sharpen the evidence review questions and they have participated on many of the calls, and have been helpful. So, I am going to first, again, summarize information about the Pompe disease. Which I think most of you know but I think it helps frame the conversation later. So Pompe is a lack of DNA which leads to a [Inaudible] it is located on the 17th chromosome. More than 300 mutations have been described. They are not all specifically associated with the disease process and there are some associations with some types but there is a wide spectrum and we'll talk about that as we go along. In terms of basic [Inaudible] overall, it effects about 1 in 40,000 births. The infantile form, which I am going to be talking about later affects about 1 in 133,000 infants based on gene studies. Delayed onset is about 1 in 26,500 or so to 1 in 57,000. Studies are underestimate the [Inaudible] because of unrecognized mutations and it is not the same of collection of cases. It is also true that the

actual induces very similar by race. And we are going be talking about that later. This figure illustrates the spectrum of Pompe disease in terms of the forms. The infantile form, which is in dark red and the lighter red, it is about a third of the cases and then the late onset form comprises the rest and the infantile form can be looked at by those with or without [Inaudible]. However, the story is a little more complicated than that, as they usually are. So in terms of case definition, Pompe disease is often broken up into two categories. There is the infantile which is considered to be the most severe. It has onset in the first year of life and can be subdivided into infantile with the presence of [Inaudible] which is the classic form. The newborns have cardiomyopathy and without treatment [Inaudible]

Operator, can you make sure all of the other lines are on mute?

Yes, ma'am.

Thank you.

And then there is the infantile onset form, without cardiomyopathy, without treatment, is death in early childhood. Again, there may be some sub clinical or hard to identify problems even in those with the non-classic form. In the late onset form, there is presentation and this is from individuals who develop onset later in life and most of them symptoms in adulthood. Since, there has been no large perspective collection of late onset cases at birth, the description here is summarized from case descriptions that are out there and things may change in the future with better identify case. But usually now, those with late onset disease have a diagnosis some eight to ten years after they get symptoms because of the slow progression. They can have mild weakness in childhood that also goes unrecognized and there are variable outcomes without treatment, ranging from becoming in wheelchairs to needing ventilators and more.

Now, what I would like to do is summarize fist the natural history of the Pompe disease. In 2006 there was an international study to describe the natural history of infantile Pompe disease. At that time, enzyme replacement therapy had become available and it was not ethical to withhold treatment . So much of what we know comes from this one study where they looked at all of the treatment centers to find cases. And when you read studies of treatment, most of them are contrasted with this natural history study. So in this the work they identify 168 subjects. Again, they were identified the in the clinic. Most of the cases had classic infantile disease, with over 90% have heart problems, and the age of development was around 2-months of age. And the median age of death was around nine months with a range of about a third of a month to a little over 73 months. Um, this is the figure from that natural history study. The figure on the left showing the survival curve for the 168 infants with Pompe disease, the figure on the right is those who have both survived and are ventilator free. And you can see the drop in the first year of life on both graphs. To help understand the figures, I created the table below that shows the survival rates at 12 months, 18 months, and at 24 months of life. So, there are a couple of other considerations that I want you to be aware of. And this is one, this is a big issue when we first reviewed Pompe disease, it is the issue of CRIM status. That is cross [Inaudible] material. Those are individuals who, they make some enzyme which may or may not

be functional. That is if you are CRIM positive. If you are negative then you make no enzyme at all. And the issue with that is if you are negative and then you get enzyme replacements, then there is a chance a chance that you could develop antibodies to the therapy which is going to make it work less. It is true and you'll see this later. Those individuals who are positive do develop, or have a risk of developing some antibodies. So that is one issue. There is another issue that we did not talk about when we first reviewed this. And this the issue of [Inaudible] to individuals who have this do not develop disease. These are individuals who make active enzymes and the function appear low or undetectable. There are two well described specific mutations that are associated with this. There is a indiscernible frequency in Taiwan affects 14.5% of individuals. And the reason that is important is because of course it could dry false positives on screens. There is a thought that the frequency is lower and I'll address that later. I will admit that mechanisms is not clear to me and this is something that we are going is there clarify with the experts as we move forward. The other thing is the genome type is not always clear. So it can be hard to predict when actually it is going to happen. The other thing is the impact of having one associated with Pompe disease is not clear after the evidence review. It does seem like there is increased frequency of having one of them associated with Pompe disease with the [Inaudible] deficiency and whether or not that modifies the disease course is not clear. So if you have late onset disease and it is that pre-disposed to developing health problems earlier. I do not know the absolute to that question. In terms of diagnosis, it is based on muscle cells. Of course, muscle is not usually biopsied because of risk. Individuals have less than 1% of normal activity associated with the infantile form. Sometimes studies talk about the enzyme activity being less than 5% and the able to diagnose enzyme activity. Again, it is important to look at [Inaudible] and that can be determined by known typing and it can help identify CRIM status, which can play into how enzyme replacement therapy is managed, for example, if there needs to be a given known therapy. Again, as you know, this is the main state of treatment. It was first licensed in 2006. There is an additional product licensed until the United States for patients eight years and older who have late onset disease. Treatment is now 20-milligrams per kilo every two weeks. It usually lasts about four hours and one of the key things to remember is that this is treatment that is required over the lifetime. So,--it is not a cure. So individuals with this disease need to undergo therapy every two weeks for the rest of their life. So one of the questions is, how many does it cost to provide that therapy? And you know, they mentioned numbers from 100,000 to $300,000 per year. In 2006, wholesale price was $750 and if you multiply that out, it is about $75 per year per kilo. That is not including the time.

And that assumes there is no wastage, but I am just trying to give you a sense of how much treatment costs. Screens are based on measurements of gas enzyme function. There is the [Inaudible] and then measurements of the function and there are several ways to measure function. For example, [Inaudible] after the enzyme requires a separate run. So this is not in the same time that you are measuring the other as sect. And then--aspect and then there is also [Inaudible] which can range from traditional to micro. There is work under way with X-ALD. And it requires more sensitive aspect machines to be able to separate out the enzyme function. So, just something to remember. This is separate equipment. And then there are other strategies that have been helped, measuring the ratios. I am going show you that when I

present Taiwan data. In terms of current screening, there is the Taiwan screening program. They have a program that I am going describe in detail. In the United States population results screening, I am presenting results of the literature review. We are going have twelve phone calls with the experts and be able to get to the critical data. So Illinois about three years ago looked at micro but that did not work out and they are now using mull multiplex. Missouri is now pilot testing screening. The states of New Jersey and new Mexico have mandates but planning is still in place. In Washington State they have an enzyme and they are in the beginning of developing pilot studies. There is also some commercial and other research going on. Perkin offers screening and the Mayo clinic is looking at different methods including [Inaudible]. So again, the things I am going be talking today are the evidence review, and then we are going to talk about where we are with the decision, the model, and then [Inaudible] is going be talking about the issues around public health readiness. In terms of the review, we looked a [Inaudible] m biopsy has a lot of the European literature that may not appear. We identified 1,982 eligible studies and questionnaire narrowed it down to the full text to look at them and at the end, we are down to 78 articles. So the purpose to, what I am going to do is show you what I think is the most important data. You should also add that we have had a series of experts to make sure we understand the literature and help with the decision tree model. So we have had four of the panel calls and you can see the names listed here of those who participated on the calls. So list let's talk about how well the screening works. Now I tell you that the Taiwan experience, as you would expect has been reported in many different studies. This is looking at one of the most recent ones. Because you know, each study includes data from the last one. So based on screening of some 473,000 odd newborns, they have had the experience that is on the left slide and I hope your screen looks bigger than mine is because I am having trouble reading my own numbers. But what I would like to point out, just a second. Full screen, there we go. Among those, of the 473,738 that have been screened, 31 were a normal and they were, after confirming story evaluation, 5 of them were normal. 17 had, going to show you here, later onset Pompe disease and nine had infantile. Now in many of the reports from Taiwan, they talk about litter onset disease which includes which we were considering the non-classic infantile. So it can be hard.

Because the reports combine these early infantile with what we were calling late onset that was caught later. As was pointed out before, Pompe disease happens over a spectrum. But we have really drawn the line and are trying to separate things. So we are going to have to talk with those involved with the Taiwan screening to look at this so you can really understand what is going on. But you can see that um, on, just a second. Next slide. That of the 473,000 who underwent the first screen, they were a little over 2,000 who had inconclusive results and who on the second drive were found to be abnormal. And--abnormal. And one of the reasons there is so many children is the rates of deficiency. So on the slide, they recalculated that would happen if they used an increased threshold and that decreases the number--decreases the number of inconclusive. There were two cases of later that were in the normal category, and again, one of fortunate things we are going to do to try to sort out what is in the later onset, what is classified as later onset. So, um, looking back on the screening data, there are several important questions that we are going to go back to the experts. What findings are available. In the Taiwan study, which is the difference between the later onset disease and how the Taiwan

experience is generalized to the United States. The next question that I would like to talk about is what benefits and harms are associated. So there is a trial, which has been described in at least three reports regarding the outcomes of the two week trial for 18 subjects, the classic infantile which was confirmed by 26 weeks of life. And there is improved survival compared to the controls which I talked about before. There was only one death and that was shortly after the trial was completed. Most did not develop. But um, I would like to point this slide out. This is again, from the Taiwan experience. Because I think it provides the best data about the benefits of treating infantile Pompe disease. So this is the survival curve. On the left there is the portion of survival and the right is increased survival which is, you can think of that as not needing ventilator management. So the numbers are small here. But what I would like to point out first is the first curve, which is that drop, are those babies that were born in the pre-enzyme replacement therapies era. And then the darker line on the top is those children with infantile Pompe disease detected through newborn screening. So you can see there is a difference all through again, the numbers are small and you know, it is all continuing. And then um, there is the intermediate curve which are five children who had CLIN-L disease--started detect the infantile disease but who were not detected in the early newborn period and then the CLIN-E. These were detected early in infancy. So I think this is the most compelling data of early detection. There is still, as with the screening, some very important questions that we need to look at. And, that is, including what is the current approach to the status and how important is the status to help outcomes? How significant is the development of antibodies? What are the harms of treatment of treated that have been identified and then how does the benefit change based on classic verses non-classic. So we are going to be exploring these with the experts. The next question I would like to talk about is what benefits and harms are associated with late onset Pompe disease. This is unclear and it is really critical--really a critical question to answer. There are many, more case reports of the effectiveness of enzyme replacement therapy for individuals with late onset disease. But it is, what we have less information on is what happens with the early identification through newborn screening of late onset disease. This is something that I hope that the Taiwan data is going to be able to inform. But really, we are going to have to consider the second social implications for parents of the early identification which could go both ways, of course. What are the costs associated? Again, cost is not a major key question. But something that we think about in terms of access, which is why we have the question, if more Pompe cases are found earlier, can patients get access to enzyme replacement therapy treatment? Access to care is an important consideration. So, the--so, the next steps for the reviews is to complete the tables and provide the quality scores to get access to unpublished data. There is also a disease registry that may help with things and then we are scheduling the expected interviews. What I would like to--expert interviews. What you would like to do is hand the presentation is Dr Lisa Prosser.

Operator, can you please allow Lisa to speak?

Please press star one, Lisa.

We'll open up Lisa's line. Again, please press star one.

Okay, your line is open.

Hello, hi.

Do I need to advance slides for her?

I do not have the power to do.

Okay, if you make a beeping noise then I'll advance the slide.

Actually, I do have the power to do that. Perfect, I am from the University of Michigan. And I am a health department economist and division analyst. The decision analysis is an approach to decision making. And it is part of the condition review process. Using this can provide an approach for evidence and can also be useful for specifying the assumptions being considered. In 2011 there was a separate panel for the condition review work group that recommended as part of the review process. So we had the uses for [Inaudible] and we'll be applying it in the consideration of Pompe disease as well. On the application of modeling to no cost--conditions that are been nominated is the development of simple models, key health outcomes--outcomes associated with screening. But for Pompe disease, we do have a research project here at the University of Michigan with Duke and other schools funded by the agencies of health care research and we are going to be looking at the cost. This project is happening parallel to the condition review process. So to the extent that we have the data available, we are going be able to bring those in and present them at the meeting in May. Cost estimation is not part of the condition review process. Reviewing, if it is available and identified, we'll produce the estimates there. But it is usually not part of the condition review process. So, going back, the goal here is to project health benefits and to be able to project ranges for outcomes that have been identified. The draft model is in development. As Dr. Kemper mentioned, we have health and expert panels to review the draft computer model and we'll modify that as needed and as we finish reviewing the available evidence. We are identifying the parameters. We'll conduct at least one more panel to review the structure, the assumptions, and the key outcomes. Once they are finalized, we are going run the model, again, focusing on ranges with the uncertainties or lack of uncertainties given the level of evidence. This slide shows the draft for the simulation model. This is probably hard to read all though it is a little bit easier to do in a webinar situation. I am not going to go through the details of the model. But I want to point out that there are two arms of the sub models within the computer similar population models, late newborns undergoing screening as shown on this slide. The next slide is going so show a similar set of newborns that are going to go through identification. Let me step back. Each box is a health state that a newborn in the model will pass through. Each arrow is a probability and again, they are going to be ranges not just estimates. There is a screening component in the upper left, once newborns complete this, they'll have a confirmed Pompe or not. We will then follow them in the similar population model until two years of life. That has been identified that we are going to be presenting in April or May. Going to move to the next slide which shows the clinical identification. Again, the structure is similar in terms of the disease process for Pompe. But what is different here are the probabilities of the different outcomes because of the

diagnosis. The newborn that we are going to be modeling are newborns that are not at an increased risk for Pompe. So that is not siblings of children who have Pompe. So this table shows the key outcomes that have been identified to date for evaluating newborn screening. The first five are the screening outcomes, so we are going be able to project for an U.S. newborn who the range of numbers of true positives, true negatives, false negatives and screens will be for a cohort. The two-year outcome cost we'll project the cases compared with clinical diagnose notice. We'll be able to classify those and later onset Pompe. We plan to project the number of cases who are anticipated to die within two years compared with clinical identification. And for those that are projected to be alive at two years, we'll also be looking at those which are going to require ventilators and those who are going to be free at that point. That is going to be key in diagnosis. So looking forward to the anticipated results, we are going to project the outcomes with the ranges. Another key result from the modeling part of the condition review will be the identification of key parameters So we vary them over the ranges from the literature or review, we can see which ones have the greatest impacts and identify those as areas that need more research. In terms of the use of the results, in addition to the key outcome using analysis, also provides transparency regarding the assumptions that go into the development of the model. So those are going documented. And again, it can helm with the knowledge gaps. So what are the keys that we do not have is good data and you can use this process to find those areas. So in terms of where we are now, we have the draft simulation model set up. We are in the process of developing the modeling parameters. We are doing review the inputs with the panel, that will likely happen in late February or early March. Once that is determined, we'll conduct the base case to obtain the ranges or outcomes.

Thank you. That was excellent. What I would like to do now is hand things off to Jelili Ojodu to talk about public health impact assessment. So we'll need to open up this line.

Yes, operator, open up the line.

One moment, please.

There, can you hear me?

Your line is open.

All right, awesome. Good afternoon or good morning. So just to be brief background of the public health impact assessment that we conducted, as many of you know in June of 2011 the Secretary of Health and Human Services charged the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children to include the public health impact assessment as part of the evidence based review for new conditions being considered for the screening panel as outlined under the Newborn Screenings Saves Lives Act. And [Inaudible] was pleased to conduct a number of surveys on public health newborn screening programs to review as noted on the screen here, the potential public health impacts of new conditions and the readiness of selected states to be able to add Pompe which is, I think the next condition that is being considered for the core panel of disorders. So to go on the test in late 2012 and we are

working on these activities as we speak. I think I would need one of you to move the slides for me. So next slide. Beautiful. No, go back one. Thank you. So I know that there have been some questions about the states, obviously, there are 51 states and states do things to their ability. And we were not going to be able to survey every state but we did want to get a good sample of the states. The selection for the states that we used are as follows. If a state is participating on a regional, so there are seven. Population size. So we divided states up into small, medium, or large. Less than 50,000, 50,000 to 150,000, and over 150,000. Some states actually have some mandate tied to a condition after it is recommended. We wanted to get a sample of those states and others as well. You know, states that outsource their newborn screening program, testing rather, there are a couple of states that do that. And other states outsource to either another state newborn screening program or a regional program. We wanted to get a sample of those as well. And then obviously, I think eight states plus another three states actually do two screens. So a first screen and then a second screen, at 10-14 days at first. So that is a general character. The condition specific factors include the lab story and analytic requirements and equipment related to screenings and then the experience with screening for similar conditions. Next slide, please. Thank you. So, with this the criteria that I just mentioned, these are the states that we picked. We have Massachusetts, Delaware, and the state of South Carolina, Illinois, Minnesota, Iowa, Nebraska, Texas, Oregon, and state of Washington. By this, we are able to get through all of the regional collaboratives. As noted here, some states have mandates tied to a the condition on the RUSP once it has been added. The states that outsource their newborn screening program is newborn screening testing, not the program. In this case, it is Nebraska, and then the population as noted here from 2009. Academic affiliation. Some states have an affiliation with a university and some do not and those are noted here. Folks, states that are doing some kind of testing, whether it is anonymous screening or have a mandate to do newborn screening for Pompe right now. So these are the characters that we used, that we are using to collect the information on the readiness and feasibility, adding Pompe to the disorders. And I am just going to talk about Webster's definition of readiness. It is important as the committee makes the final decision at the end--at the end of the day, it is prepared for some experience or action. Feasibility is defined as capable of being used or dealt with successfully. Let's keep that in the back of our minds when we talk about the next couple of slides here. Next, please. Beautiful. So, um, the data is going be in two stages. The first stage is a survey that we have already administered to the ten states that were shown on the last slide. We have actually completed almost all of the surveys. We have a 90% completion rate at this point and the final states will be completing the survey shortly. The second stage is to conduct a semi-structured in-depth interview. We are going to call and spend an hour with the states to do an in-depth interview with representatives of the program to get in-depth answers on some of the question that is we are asking. That will proceed; hopefully in the next several months prior to when you are all going to be making that final decision on Pompe. Next, please. So just, this is just to show the results from the survey. 56% of the states or newborn screening surveys, and it is now nine states. They take between six months and a year to make a decision to get a condition. Not necessarily Pompe but any condition once the process is started. 22%. This is just one program testing for Pompe, I am sorry, two programs out of the nine currently test for Pompe using anonymous samples. And then 11% of the newborn screening programs survey are investigating the theory, that is one program, of screening Pompe but have not yet

tested any samples yet. Next please. A good amount of the states, as you can see, responded that they do not screen for Pompe in any fashion. 67% of them are not investigating routine screening for Pompe and six of nine of them, or 66% of the states do not have authority to implement screening for Pompe at the moment. Some challenges that we found from the results that we have not dealt in yet, but we will, are funding and staffing and laboratory staff. Now, the survey did ask a number of questions related to processing and getting approval, condition specific questions, the process for implementation and then other resource considerations as it relates. 56% of the states surveyed could implement screening for Pompe six months to a year understand with the hurdles they noted in the survey are cleared. So that is interesting and a good point to note. Next, please. This is where I talk about the next steps. We just started, as I noted and we are going to be collecting them, we will be planning to collect the last states information so that we have a total of ten states that we are surveying. The next step is to do the in-depth phone survey and get more information on the readiness and feasibility of the public health impact of adding Pompe disease to the uniform screening panel. So, um, I think this is the time that I pass it back to Alex.

So, thank you very much. And yeah, I just want to echo what you just said, um, the surveys that we sent out, so far the call tricks online just provide basic information to allow the deeper guide that is going to go on during the interviews with states to understand what is going on. That information is going be supplemented by the handle that we are going to around the tests and so forth. There are a number of difference ways to do the screening. We just have to figure out exactly what the issues are with each of them. So, um--again, summarize now what we have learned and what we need to fill in from the experts and other data sources. We talked about the modeling that she is doing and she talked about where we are with the public health assessment, so it is our goal to be able to fill in the gaps and have things presented at the main meeting. But if there is any guidance that you want to us look into. I guess that members have to reflect on things after the presentation as well, but any guidance about areas where you would like us to focus or something that we did not mention that needs detail would help, given our shortened goal in terms of time.

Well, we want to make sure that you all have the chance to complete the evidence review in such a way that you are comfortable.

We are not going to take shortcuts, but we may not have done things.

Right. So let’s leave phones open--and then, let's hear some questions or comments or some direction from committee members first.

Operator, if you could open the lines, please.

Yes, ma’am.

Can you hear me?

Yes.

I have a compliment on the work. Just a suggestion, when you contact the health departments for their, that one hour interview, if you could ask them where this would fit in the queue, if this is a state that has not done heart disease, and where this would [Inaudible] getting the other conditions going would impact their ability to do Pompe.

That is a great point. This does not happen in a vacuum.

Will do. Thank you.

Alex, this is Don. Will you be reporting your reported outcomes in terms of survival? Will you be reporting other types of long term outcomes as well?

Yes, there is a fair amount of work that has gone in development, and motor develop. For the group presentation, I did not present that information, but it is available. It is going to be in the report and I can highlight that in April.

Thank you.

This is Jeff. Alex, can you outline what the clinical implications are kids with late onset versus individuals in the newborn period?

I wish I could. So what I was hoping, you know, I was hoping at least to find a published protocol about children in the published literature. So that is something that I am hoping we can get from the Taiwan program. But um, so long, or I guess the short answer is that I cannot outline it based on the evidence that we have uncovered so far.

This is [Inaudible]. I have a couple of questions and well, actually two suggestions and a question. The question is what about the readiness for follow up on the clinical side. Is that being investigated, too?

Yes, sir, it is.

And I try to get it, too.

Yes, and this is Sara. When you speak, please identify yourselves.

Yes, sir we are adding the questions. So the accessibility to treatment and other activities related to the management of the condition. So yes. [Captioners transitioning]

Is really considering to just do Pompe, or to do this right away with other conditions, given that most of the assays that happened to do the screening are multiplex meaning you can screen for more than one condition? This is Alex. Sara is making sure that I say my name. So um, from the

educational side of things, we were going to--evidence side of things we were going talk to the Missouri program to see how the process works. So I'll have that information for you. The states that are screening for Pompe disease are multiplexing it to other places. Because it is a multiplex test, how much do you want to hear about the other storage disorders? It muddies things and makes it harder for us, because the way the committee is working is one condition at a time.

[Captioners transitioning]

I will provide information and the non-Pompe screening activities.

That is fine.

Is that sufficient for you.

Thanks.

Additional questions from the committee let's open it to their liaisons as well.

All right.

I wore everyone out of the matrix.

A significant amount of progress has been made and all three of the participants, I think we are well on our way with the data. I have this thing is enough to make a decision and it seems to have gotten along very nicely for your efforts.

Thank you very much.

This is Alex, saying thank you.

All right. Any additional comments? If not, we are 10 min. ahead of schedule. Our plan now is Meredith Weaver, can you ask her to press* and the number one and ask the operator to open her phone line and mute everybody else

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I am going to take one second to mute everyone a 90 the person that wants to have that line open. Hold on one second. Okay. The person needs to speak right now, please press star one.

Are you available?

Let me introduce Dr. Meredith Weaver. So remember talking about the population-based screening done by Dr. Meredith Weaver. Dr. Weaver is a board-certified genetic counselor and associate project counselor, coordinating implementation of the work unit study now on the analysis phase and genetic services directory and is collating and expanded comp population-

based policy recommendation. Dr. Weaver has worked as a pediatric and adult genetic counselor at the University of Maryland where she held a faculty appointment with the genetics counseling graduate program from 2006 through 2011.

This is Meredith Weaver and I'm going to talk about the report from a population-based screening, which is a group of 29 individuals, and I only have 10 slides because I think the timeslot is to be used mostly for discussion.

I'm just going to start with a brief history of the project and the timeline as refresher. This began in May 2010 upon request from the committee. The workgroup I am referring to together present additional information on the issue, and on August 2010 to administer the data protection analysis report preparation under the guidance of Dr. Copeland. About two years ago we had the first and only in-person meeting where we decided on the criteria for each issue, and the desirability and feasibility and importance. The data collection occurred in the middle of 2011, in the first round of the survey was in April, in the second round and May and June. The first report on their results came in May of 2012 to the committee, and that is only did I dates and gave an assessment of where we were, then analyzed the data. Then, most recently in September, I gave an interim report which was a 30,000 foot view of the results, and at that point recommendations had not been focusing on the results. Here is a list of the members of the workgroup and I wanted to thank these members because some people had to do work after hours or on the weekend, and that effort is certainly appreciated.

So today's call, we have a discussion about the merits of sending this report to the Secretary of HHS, as it is ours for the revision and reframing. And before we do that, I want to give you some highlights and benefits possible to have the report on and have the slides up. So I'm going to give the background of the report in case we can have them both on the screen at the same time, pages 10 through 14 of the report, and the consensus was defined as more than 75% with the agreement of the majority of the opinion. We found that there was consensus; it merits the general principles of carrier screening. So for example, table 1 is on page 10 and we summarize the social issues and things like informed consent, knowledge of conflict of interest, insurance coverage, and those types of things which people are pretty familiar with matters with the areas of consensus were. Contrast areas of non-consistent consensus related to evolving technologies and moving them into public health domain and people, to have differing opinions and that is where people wrote more into the text boxes and had strong opinions. So finally, the recommendations are summarized on the next slide and this is pages 30 through 32 of the report and the recommendations in terms of the five different topic domains, the social issue domain was desirable to consider these that work. With variation in how feasible they might be to examine further and that is where the non-consensus was, is this easy to do or is it going to move mountains and order to examine. Is it desirable to consider economic issues are how feasible that might be there psychological issues to consider prior to administering screening and psychological support available to the person. What are the positive implications of using the information that was learned from the screening, misperceptions, the risk of those types of things, and education and prior to administering any kind of screening and educating the public, educating healthcare professionals, those types of things. It is desirable and important to

consider many testing issues. This is the largest section of the survey with variation in how feasible it is, so people agree that we need to consider these things. It is desirable and important but again how easy is it to do this? So the points to consider, these were the overarching issues when conducting a population-based carrier screening program there were general to the screening process and condition specific. So people commented in the general sense as follows in particular conditions they had in mind. And again, it is not a list of which conditions for anyone to screen, does the points to consider. So today, the discussion is about the chosen or proposed form of communication to pursue the context of this report and the committee's affirmation of the value recommendations and actions would be to forward the project to the Secretary for Reformation purposes only. Top option is official support and the third option is acknowledgment.

In terms of degree, report and present form as a FYI are based on things we talked enough today, and discussion points one and developing appropriate capacities as a foundation for future committee conversations about the challenges of living carrier education from a clinical service and the public health of population wide domain and so those are just some things that I thought we could start with. That is my last slide.

Thank you for the presentation I am going to ask Sara for a couple of comments before reopening this to general discussion.

Yes. This is Sara. I was charged with this a couple of years ago. The Advisory Committee requested a report this was during the era of direct to consumer testing, and it was CVS or Walgreens looking at offering something over-the-counter, and there was a lot of concern about the considerations that need to be taken when looking at genome sequencing and what you're going to identify and also carrier screening. However, there was never an intention to come up with a panel because I think that there is too much variability in terms of population impacted, etc. and the shudder to think trying to do that, this is just some guidelines if a population or a group thinks it is important to start screening for carrier screenings for certain disorders, one of the considerations that need to be taking into account to provide a framework of questions to ask and issues that need answers before starting.

Thank you. Let's open the questions, first to committee members so we can make sure the lines are open. We can go ahead and start the discussion.

All lines are open and interactive.

Let's open to committee members first.

This is Cathy. And this is just a process question that I have, but will this document be available for groups to consider if they are moving forward, and is posted on the website. Is that what would happen with this?

At minimum, it would be posted on the website and it can be freely distributed. I think Meredith was also hoping to put a summary of publication as well, to get the news out there a bit more. But, we did want to start a publication until we had to review by the advisory committee, so it is freely available and open for consideration.

This is Alexis Thompson, as you are crafting this, I appreciate it some perspective on when the environmental document was first initiated. I think that really is important and I can't help but in my own daily work be struck by how useful this document would have been prior to action by the NCAA, and obviously one of the most prevalent trade conditions which is out there to a certain extent in the public domain. I guess the question I have, as the committee was drafting this, was there any test of any particular conditions, to examine whether or not what you are proposing, and it was likely to occur in the student issues being addressed? Necessary asking if we ran a specific disorder. The gamut?

For instance, the document sounds like it has a lot of great fundamentals and the question would be, is there any condition where we can look to, is the bar too high, is that the expectation that we were to initiate population-based screening that condition would need to address all of those issues, is that what we are proposing with this document?

I don't think it is the set standard. I think it provides a framework where there are questions and that is what it is for. It is not to say, you can do this, don't do this. It is, rather, to say here is what concerns were raised. Here are some questions you should answer before you start implementing this, just so you know what the pitfalls might be. And we did not run the specific condition but we did have several condition specific advocates, in particular FMA, so we tried to get a variety of perspectives. I also had a Rabbi from the Jewish community, and they have failed to find population-based carrier screening to contribute to this as well.

I guess I am surprised that we are trying to provide structure for diseases and I am surprised that we would not want to have something similar since we are talking about carrier screening. Strictly there is some value looking at this process and I guess I am surprised that there would be some value with something comparable in less detail for carrier status.

I think that carrier screening is a Pandora's box, and there are so many different reasons to do it, that at this point in time that wasn't the intention. At a later point in time, if a specific question or two, for consideration this provides a framework for that. But we definitely didn't want to get into the business of making recommendations for carrier-based screenings partly because there are so many populations that have different risk factors that change the environment.

Thank you.

Additional questions?

We will move to the liaisons for additional questions.

This is Alan Guttmacher - I would raise a strategic question the reports are fine, and the strategic question for me is that I'm not sure exactly what we achieved by simply acknowledging it and posting it to our website, and wisdom of a diverse group of stakeholders about this. I am not sure if that is the Secretary to be aware of particularly that warrants necessarily that level of that we shouldn't hold our fire for saying so we definitely want the Secretary to act on or do something with so just a strategic question.

That is a very good point and the reason for forwarding it to the Secretary and more of these issues are going to be coming to her, not necessarily the advisory committee, that genome sequencing goes forward. They started to examine these issues, and it is conventional wisdom and if you're in genetics. However, if you are not in genetics, something she can turn referred to others. I am not married to having it sent for to the Secretary but they think it is behind the request.

I'm not going forward, just discussing it, it is a close call one way or the other.

More, specifically related to the Secretary as an FYI?

This is Carla - we have some discussion about this as well and we would ask the same question that Alan just asked, what purpose would it serve to send it to the Secretary, what kind of response would you like. She does get a lot of requests and we want to make sure, when she is sitting with her advisor she knows what the next step is. She was given this particular document for there are issues that might come your way, and so we think it would be clear to her to understand the context. Also, reformatting the document in a user-friendly format because again, the Secretary and people may not be geneticists, and they need to have it be easy to understand, and be right in their face. This is what you can do with it and other situations, and that will be really easy for decision-making.

This is an opportunity for us to reformat some of the executive summary. A really nice place to put that for the framework of the reason, and the ideology for all of the subprime. The Secretary is not the only audience, that would be useful for general audiences, which is why it is up on the website and that kind of background would be very useful.

I would agree with the last couple of remarks - if you could make an executive summary and the audio is not anonymous, at least not as deep into this is some of the folks in the community. For instance, make the take-home messages clear, I think that would improve.

Additional comments? Related to this?

Additional comments or questions?

This is Cate Walsh. I was wondering, in the development of this document, was consideration given to the potential to identify individuals who are affected with some of the conditions for

which they are being done, because of expanded phenotype onset condition, and about that in the document.

This is Sara, I can't answer that.

This is merited, people were asked to ask about presymptomatic testing and identifying affected individuals that can certainly, even though we did not collect data that can be something that is part of the background or something.

Related to what Cate just brought up, in the background would be important in context to make sure that the nongenetic audience understands the distinction between the presymptomatic, the possibility of picking up affected individuals and carrier testing. This is focused on carrier testing and this is complicated enough, and is only part of the questions that would need to be asked for presymptomatic testing, and also to make sure the context includes the issues of planning carriers actually could be at risk for symptoms so it is not just for reproductive.

This is merited, that makes sense.

Okay. I am sorry I did not hear the last comment.

This is Meredith, I said sure, that makes sense.

Thank you Meredith.

Go ahead, if someone else is going to say something. I'm sorry.

This is Sara, it sounds like we need to do some more tweaking on the executive summary and the introductions and we can bring this up for discussion in the next meeting, does not need to be finished now. But it is nice to see a light at the end of the tunnel for this particular project so Meredith, are you okay with that?

That is fine.

We don't need to have a vote today.

That makes sense. The feedback from the committee has been good and helpful in focusing the strengths of this report and how it can best be utilized so I think that has been good. We will postpone the vote, and have some additional work be done and April or May, we hope to see you again.

Or September.

Depending on the time frame, this is Sara again, we may be asking members on the committee to help us with framing this executive summary and the genetic expertise. It is nice to have more than one set of eyes taking a look at it.

I think that is a good idea.

And you certainly will ask for volunteers and point out some points to some individuals who may be selected to help out.

This is Ed from the March of Dimes. I just want to mention that for possible publications, I am editor-in-chief of Molecular Genetics and Metabolism, which is the official journal for alcoholic disease and I am certainly interested in these issues. I would be happy to talk off-line with people to see about perhaps doing it in parallel with the document for the Secretary something that could go to publication.

That is wonderful.

Okay.

Will you get in touch with me about this?

I will ask you to get in touch, so that I can do that.

Okay thank you.

Great.

Additional comments?

Okay thank you very much. Meredith you were very efficient with your time.

We are half an hour ahead of schedule. So this is good,
So I think we all need a break. We will take a 15 min. break and we can start the subcommittee webinars a half an hour early.

That might be an issue for some people.

Okay. That is an issue. Let's take a longer break and start the subcommittee meeting as scheduled at 45 min. after the hour, and your respective time zones. For the subcommittees, please review the guidance on how to attend the subcommittee webinar, it is hosted on the webinar screen and remember, have your logon credentials ready and follow the guidance that will be on your screen so that you can get into each of the meetings. We will close today's session and then we will meet again tomorrow morning at 9:30 am eastern time as a full committee again. I want to thank everybody for their input, and I think that is good and we will

see what we might have done better and determine effective [Indiscernible] this kind of format. Everybody enjoy an extra break and you can attend your subcommittee meetings as scheduled. Thank you very much and we will talk you tomorrow.

Thank you.

[Event concluded]