Transcript: Friday – May 17

Morning Session

Please stand by for real-time captions.

Welcome and thank you for standing by. At this time, all participants are in listen-only mode until question and answer.

At that time, to ask a question, press star one on your phone. I will turn the conference to your host, Dr. Bocchini. Sir, you may begin.

Thank you and welcome back to the first meeting of the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. There's a couple of housekeeping notes before we get started. For committee members, your sound will be coming through your phone lines. Please make sure that you have your computer speakers turned off. Hold questions and comments until the end of each presentation. When invited to speak, please state your name each time and speak clearly to ensure proper recording for the committee transcript and minutes. Press star zero if you have problems with your phone line. For members of the public, sound will come through your computer speakers. Then make sure you have your computer speakers turned on. Now, we will conduct roll call.

Alphabetical order. Don Bailey. Coleen Boyle.

I'm here.

Denise Dougherty. Melissa Parisi is here. Charlie Homer? Kellie Kelm?

Here.

Fred Lorey? Michael Lu?

Here.

Dietrich Matern?

Here.

Kathy Wicklund? Here.

Andrea Williams? Here.

And Debi Sarkar is in the room with me. Jeff by Ken will not be present at today's meeting. Let's go back. Don Bailey?

I'm here.

Charlie Homer?

I'm here, thank you.

Fred Lorey?

American Academy of Family Physicians. Frederick Chen?

Here.

Beth Tarini?

Here.

Michael Watson?

Here.

American College of Obstetricians and Gynecologists, Nancy Rose? Association of Maternal and Child Health Programs, Lacy Fehrenbach? Association of Public Health Laboratories, Susan Tanksley?

I am here.

Association of State and Territorial Health Officials, Chris Kus?

I'm here.

Department of Defense, Adam Kanis?

I'm here.

Generic -- Genetic Alliance, Natasha Bonhomme?

I'm here.

March of Dimes? Edward McCabe?

I'm here. National Society of Genetic Counselors, Cate Walsh Lockley?

I'm here.

Society for Inherited Metabolic Disorders? Day two is Georgianne Arnold.
Let's go back and see if Fred Lorey has joined. Nancy Rose? Lacy Fehrenbach?

This is Lacy Fehrenbach. Can you hear me?

Yes. We can hear you now. Georgianne Arnold? Okay. Now that the roll call is complete, we will go to the public comment period of the meeting. Before we begin hearing public comments, I would like to acknowledge all of the written letters of support for adding Pompe disease, not only for this meeting, but also for the previous meetings in January and in April 2013. Written public comments that have been submitted for this meeting can be downloaded, via the webinar pod titled written public comments. Today, we have individuals who wish to make oral comments. They are queued on the phone line and for those of you who are making oral comments, please make sure you have your computer speakers turned off and keep your phone on mute unless speaking. If you do not have a mute button, press star 6 to mute your phone. Before speaking, please state your name and organization, if applicable. Operator, please open the line for Dean Suhr, the first on our list of public comments. His organization affiliation is the Metachromatic Leukodystrophy Foundation. Mr.Suhr?

Good morning. Can you hear me?

Yes, we can hear you.

Excellent. Yes. My name is Dean Suhr and the organization does represent Metachromatic Leukodystrophy but we call ourselves the MLD foundation. I do want to continue to thank the committee, as you reorganized and restructured through this time of change. We do appreciate your work and your persistence, thank you for that. I am going to very briefly repeat some comments that I made in a couple of the previous meetings or comments. That is related to the criteria for adding a screen to the newborn panel. I'm interested in convening a town hall, related to the criteria, that there be a viable therapy before a newborn screen is approved. I recognize the process and there's a lot of viewpoints on that. Certainly, I don't understand or know of all of them and I'd like to continue on this path, in the last month or so since the last meeting, of the opportunity to talk to folks from industry, a couple of folks involved in the Secretary's Advisory Committee and some other advocacy organizations. This seems to be general interest in this discussion. With that in mind, I just want to keep this up on the radar. As we get something on the agenda, not on your agenda, probably another meeting of sorts. Just so everybody can share their perspective and their insight. Then, we can decide whether this is something worth pursuing. It's probably something that won't happen for another six or eight months or so, just we can get all the parties engaged. I do want to keep that on the radar. The lack of a viable therapy is not necessarily a bad reason to detect that somebody had the disease. There's always something you can do for these young children, in terms of just quality of life care and knowing that they have a disease, will prevent diagnostic odysseys and perhaps

improve quality of life, not only for the infant, but for the family. So, that's kind of the general basis of our interest. With that, I thank you for your time and your hard work.

Thank you Mr. Suhr. We appreciate your comments. Next on the list is Ms. Tiffany House, who is representing acid melt his deficiency Association. Ms. House?

My name is Tiffany house. I am the President of the Acid Maltese Deficiency Association and also the vice chair of the International Association. I'm also a Pompe patient. I'm speaking today on behalf of all Pompe patients to request that this committee vote on Pompe disease to the Federal newborn screening panel for all patients. As Francis Bacon said, “knowledge is power.” Today, I'm asking you to empower Pompe patients by voting in favor of the diagnosis and knowledge that we have, newborns screening. During the public comments of the January 2013 meeting, I spoke about the diagnostic odysseys that patients with Pompe face. For infantile onset patients, it can be fatal. Newborn screening for infantile onset can literally save these children's lives. Early knowledge of the diagnosis will empower physicians to make proper treatment decisions and save their lives and give them better outcomes. The effect of the delay in diagnosis may not be as transparent for late onset patients, but it is so devastating. For late onset patients, the average time it takes the patient to receive a diagnosis once they start looking is 10 years. It is 10 years of damage being done to our body, 10 years of emotional and psychological distress searching for answers. I was born in 1983. As a child, I achieved major milestones but often at a delayed age. I had more difficulty with physical activity and often struggled to keep up with my peers. My parents took me to numerous doctors from the time I was 1 until I was 11, to no avail. They all said it's normal for her. It wasn't. I had Pompe and we just didn't know it yet. By the time I was diagnosed, my lung function had already been severely affected by Pompe, to 40% of normal. In addition I was starting to have significant difficulties and started to develop pleurisy. Even so, we didn't know I had Pompe for the first 11 years of my life. It was apparently doing irreparable damage. Today, even with treatment, my lungs are only at 20% and I am confined to a wheelchair. My story is not unique. Many of us [indiscernible] known about the diagnosis sooner. If only we had known sooner we could've started treatment before irreversible damage was done. It's only we had known -- and adjusted diet, exercise so we were not contributing to the damage Pompe was doing to our bodies. If only we had known sooner, maybe we wouldn't have felt alienated because we couldn't physically keep up with our school peers. If only, if only. Today, you have the ability to empower future generations of Pompe patients. The knowledge about the diagnosis has to wait years searching for answers. Instead, they will be able, in that time, to educate themselves and their families on their disease. This knowledge -- they will be empowered to make informed decisions on their life and medical treatment. And won't find out too late that Pompe has been silently destroying their bodies while they search for answers. As a national and international Pompe patient advocate, and as a Pompe patient myself, I ask you to please add Pompe disease to the Federal newborn screening panel. This test will save lives. It will allow infantile onset patients to be identified so that treatment can be initiated before it is too late, and late onset patients can be identified and avoid the diagnostic odysseys that results in years of searching and unanswered questions, only to find the answers after there's been significant and sometimes irreversible damage. Newborn screening for Pompe will change lives for countless

people for the better by giving us the knowledge we need. Thank you very much for your time and the opportunity to address the committee.

Tiffany, thank you very much for your comments. We appreciate your courage and your willingness to share your personal story with the committee. Thank you. Next is Alicia Blackington, affiliated with the United Pompe foundation. Alicia?

Can you hear me?

Yes, we can.

I'm from California. I don't want to waste valuable Committee time. Tiffany House eloquently stated the journey that we all face. My own personal story, I am 47 years old and a late onset patient. I started having trouble in 2001, and it basically took me over a year and a half, close to two years, for specialists throughout San Diego County, thousands of dollars, not knowing what was wrong with me. The fear, the emotions, until finally we traveled to the Mayo Clinic in Rochester, Minnesota to see the world-famous Dr. Andrea [inaudible]. Upon my appointment, he immediately said you have Pompe Disease. We were very afraid, but he encouraged me, that there is currently treatment in the works, clinical trials. Upon my diagnosis, I immediately found the AMDA, Tiffany House and her family. I engaged in all three clinical trials, for my desperation to be involved and to stop the progression of the disease. Had we known sooner, my husband and I would have made different choices in our lives. Now, with the irreparable damage that Pompe has done to my body, we chose not to have a child because my life was more important. We ended up selling our business because it was taking too much out of me on a daily basis. I dropped down to 80 pounds, happily, and say I'm now up to 95 and gaining weight and strength every day. I cannot express the need for the board screening with children and infants. I mentor on a daily basis, newly diagnosed late onset patients and once again, as Tiffany said, a long journey for a diagnosis can raise anywhere from months up until 10 years. Now, the damage is done. If we had only known at the beginning, we could make them decisions on the care of our lives. Just as Angelina Jolie has come forward and done with herself. Being courageous, having the power and knowledge is worth -- is priceless. So, please, committee, would you consider adding Pompe to newborn screening box we can save these children's lives and future adult with Pompe Disease. Thank you for your time.

Thank you for your courage, and for sharing your stories of diagnosis and now your efforts to manage Pompe Disease. Next on the public comment list is Doctor Priya Kishnani on from Duke University Medical Center.

Good morning, and thank you again for allowing me an opportunity to speak here this morning. I just wanted to give a little bit of my background. I have been in the field of diseases, and more specifically for Pompe Disease, for the past 22 years. My mentor is Dr. [indiscernible] whom I think many of you know, played a very significant role in the development of the [indiscernible] of Pompe Disease. When I first found my career, it really started with delivering this news to the families, infantile families and saying there was nothing we could do. The best we could do

was a prenatal diagnosis for a future pregnancy, so they could make appropriate choices. For the patients with the late onset Pompe Disease, which I want to go back to this nomenclature as I talk through this, is I don't want to minimize what results. I think you heard from Ms. Blackington as well as from Ms. House, of what it does to these individuals. I think beyond even the physical issues of being in a wheelchair and being on a ventilator, I think from a social perspective, from an emotional perspective, I think this is an area which has not been adequately looked at for these individuals. Isolation, broken homes, challenges in the school or work setting of them not functioning, for reasons that are not clear to everyone because of a lack of diagnosis. So, I want to take this through 2006, when the drug was approved and we were very happy and excited that we were changing the lives of babies with Pompe Disease, because that was where the focus was with the amount of enzyme that was available. At that time, I remember saying that if you pick them up at less than six months of age, that it's these babies are on a ventilator. We've done them a huge service and the outcome is very good. If you look at our own publications and publications from across the globe, you see that in the first year of life, with the first 18 months of life, or even the first three years of life, for these babies, the outcome is very good. It is lifesaving. These children have been able to walk. Then, after that, you start seeing the inevitable, that they are now experiencing the long-term infantile survivors. They are declining. Many of them actually just plateau, many of them declined. I think the committee had raised a few questions which I want to address today. First of all, I think that the diagnosis under six months of age, even at two months of age, is already too late. I say this not only on the clinical follow-up, but now we spend time, myself and others in the field, looking at Systolic G, looking at some situations of autopsy, of babies from two months till over that age, whether it's completely glycogen laden. They are already terminally damaged by birth and even if you were to start someone at two months or three months, it's really late. The second thing, I think, when we had nominated Pompe for newborn screening in 2006, I have to admit there was a lot of [indiscernible]. At that time, it was just emerging on the subset of patients who were negative and the ones who developed these high sustained antibody tiers and they decline. Now, we have a complete way, I would say. With these cases by mutation analysis, which the turnaround is two or three days and instead of having one or two that's in -- now we have numerous labs that can turn this information around. We have a database available which gives this information on the mutation and so we can pick up the negative babies right at the point of diagnosis, treat them with what we call immune therapy over a period of five weeks, which is very safely tolerated and we have experience of over 25 cases. I'm sure Doctor will speak with that as part of his evaluation and work up for the evidence review. So, we have definitely addressed this one major question, which was, can we really handle the true negative cases? The next point I want to make, we also now have histology data from babies who were treated at a week of age to 10 days of age and now five and six years old, those who were treated in a spotted clinical trial all as part of clinical care at six-month, for months, three months. There is follow-up histology; that is a huge difference. The ones that were treated later, at the histological level, have so much damage when you see them now it five or six years, as compared to those who were picked up and treated. These were picked up early because of a family history or sibling that died with the disease. Those patients look not only different clinically, but even at histological levels. So, those are the points I want to make for the infantile category, which I think really is, in my mind, and I'm hoping in

the minds of everyone. It's not about that, those babies deserve treatment within the first few days of life. The second category that I really want to address is the one of late onset Pompe Disease. Really going back to the nomenclature, I think late onset Pompe Disease is a misnomer. It's everything outside of classic rank and file Pompe Disease. When someone is born in the first year of life and without cardiac involvement, but can have significant pulmonary compromise and within three years of event dependent, called late onset Pompe Disease. So, I think if we keep that and think about this as a spectrum. Many, many patients, even who are considered as the old terminology, adult onset Pompe Disease, if you go back and look at the history and go back and ask them the question, their symptoms have started very often as young children. For reasons, that we could not explain why, they were not able to function like their peers. So, that is one of the key points I want to make what late onset Pompe Disease. The second is there are significant morbidity, that is early mortality. I think there is emerging data for this. The other part is that, given some of the information that we have from the Taiwan screening program of late onset—as I call them—you once again start seeing evidence of damage very, very early on. They may not have the symptoms of the disease or they clearly have the signs of the disease, with increase in PK they have evidence of tyke -- glycogen accumulation and some of the studies have been done there is evidence of damage. I think the committee may ask the question—are we ready for considering this for newborn screening? I think we've addressed many, many of the invaluable questions that were raised by the committee in 2006, and then in follow-up in 2008. If, through the years, we've understood the role of genotype and phenotype, I think it's very clear. We can predict by genotype which patients are going to have classic infantile, for the rest of the spectrum it's more of a hardship. But, we can buy evaluation of these patients, Tal in the clinical spectrum where they are. I think the second point is that what I was trying to say, is the question of Acetyl -- pseudodeficiency. We have information about this. We can deal with it and we know what to do with these patients. The third is, you know, are they good—the screen for Pompe Disease at this point, and we have evidence that the false positive rate is extremely low and very much in keeping with what would be acceptable for newborn screening. Once again, I'm sure that Dr. Kemper is going to speak with this. The fourth question, really, was do we have newborn screening data available from the United States? Yes, we do, now. We have [indiscernible], which has started newborn screening for Pompe Disease and if I have my information correct, I think there were seven situations that came up. One was classic infantile, one was a typical infantile, one that was a late onset Pompe, one which was a pseudodeficiency and one was identified to be a carrier. We had all the pieces that were very vetted questions that the committee had raised. On a personal level, all I can tell you, is that care for more than 250 patients, 300 patients around the globe and the FEMA that's recurrent is the following. For the infantile, I wish the baby was diagnosed earlier, so there was a better chance for life. For the late onset the same thing, I wish I knew the diagnosis earlier so I could have made family choices or decisions about how I could function in society. I appeal from her small perspective but also from a professional perspective. I've dedicated my career and life to the care of individuals with Pompe Disease and it would not mean anything more for me to say that this is a much, much needed area to have newborn screening. I think we have the tools for newborn screening, we have the data needed to support newborn screening. I really sincerely hope that the committee can vote in the positive today. Thank you.

Thank you, we appreciate your contributions for the development of therapy—we appreciate your involvement, thank you. That will close the public comment portion of the meeting, and now we will go into the final presentation of the final evidence review for this. We have three presentations which we will do back to back from the physician review workgroup. And I think it would be best for the presentations to be completed, and then to open the discussion for questions from the committee. The three presenters for evidence review would be Alex Kemper. He leads the condition review workgroup and as a pediatrician and serves as Director on Health Services Research at Duke University. His research focuses on the implementation and evaluation of screening programs for children, including newborn screening, visual impairment, and screening for lead poisoning. Dr. Kemper is an Associate Editor for *Pediatrics* a publication of the American Academy of pediatrics. Second presenter will be Dr. Lisa Prosser. Dr. Prosser is an Associate Professor in the Department of Pediatrics at the medical school and in the Department of Health Management and Policy at the School of Public health at the University of Michigan. Her recent work has focused on influenza vaccination, newborn screening and childhood obesity. Dr. Prosser has contributed to evidence review processes for both childhood and adult intervention, and her research evaluating the cost-effectiveness of influenza vaccination programs has been used in the development of the national vaccine recommendations. Third is Mr. Jelili Ojodu. He is the director of the Newborn Screening and Genetics Program at the Association of Public Health Laboratories. He is also Project Director for the Newborn Screening Technical Assistance and Evaluation Programs, NewSTEPs, providing guidance and direction for the newborn screening, genetics and public health. I will turn the presentation now over to him Dr. Kemper. Alex?

Think you very much. I will wait a second while the slides load. I will tell you the members of the condition review workgroup are pleased to present the summary of our findings for newborn screening for Pompe Disease, and really before going further I want to thank all the members of the Condition Review Workgroup, all of whom are very dedicated and assisted greatly in the development of this material. Our plan for today is I will summarize key findings from systematic evidence review. This is the material that was sent out two weeks ago. I'm going to highlight key findings and I have new information I will be providing for you this afternoon. The second component will be, Dr. Prosser will present findings from the projected population-level benefits from the evidence review through decision analysis, and then finally Jelili Ojodu will present the summary of the current capacity of screening programs to offer comprehensive screening for Pompe Disease. Before I go further, I want to remind people that the work at Duke University, which is the same institution as Dr. Kishnani, who nominated this condition for review. With that, let's begin by first talking about what Pompe Disease is. As we have discussed before, Pompe Disease is caused by a deficiency of acid α-glucosidase, which leads to the accumulation of lysomal glycogen. It's a autosomal receptive disorder. Many mutations have now been described and one of the key things to remember is that there is a broad spectrum of ailments. Next slide please.

As Dr. Kishnani said in her comments, we classify Pompe Disease into two large categories. The first is the infantile form, which is the most severe form of Pompe Disease. It has onset in the

first year of life, and can be further subdivided into two forms. Infantile-onset with cardiomyopathy is the classic form. In the rest of this talk, if I mentioned classic infantile-onset Pompe Disease I am referring to patients who have cardiomyopathy in their first year of life. It's associated with progressive hypertonia and cardiomyopathy, and without treatment death is usually in the first year of life. Also infantile-onset without cardiomyopathy, the so-called non-classic form. So, as you can surmise, there is typically no cardiomyopathy. There is longer survival but without treatment death is usually in early childhood. The second large category of Pompe Disease is the so-called late onset form, and that has a variable presentation. By the definition we are using it has clinical onset after one year of life. There's a wide spectrum of presentation. So from the studies of late onset disease, from the Pompe disease registry, what we know is that most individuals with late onset disease seek care in adulthood, and it often takes between eight and 10 years before a diagnosis is established, and average death is about 27 years later. However, I will use evidence in a little bit, one can also have late onset disease in early childhood. In general, late onset disease is associated with mild weakness that can go unrecognized as fully progressive myopathy and variable long-term outcomes without treatments ranging from wheelchair dependent, ventilator assistance and ultimately respiratory failure.

There are a few other factors that I want to the clear about before we dive into the evidence. First, as an autosomal recessive disorder, there are carriers. Carriers can have below normal GAA enzyme activity level and can therefore be identified through screening. Another complication is pseudodeficiency. These are individuals who have low measured GAA enzyme activity level, but it doesn't lead to Pompe Disease. These are individuals, if you were measured their enzyme activity level of blood, it would appear very low but they would otherwise be healthy. There is a high frequency of pseudodeficiency in the Asian population, high as 3.9%. Pseudodeficiency is associated with two specific nations, and can therefore be identified and diagnosed through genotyping. The other factor that I want to discuss, before we go into the evidence, is the CRIM status, cross reacting immunological material, and individuals can be classified as positive or negative. The key point to remember here is that some individuals make some endogenous enzyme, which may or may not be functional. If you make any enzyme, even if it doesn't work, then you are CRIM positive. If you don't make any enzyme whatsoever, that is negative. Individuals who are negative can develop high titres of antibodies that neutralize enzyme replacement therapy, leading to poor outcomes. The status historically was diagnosed through Western blot. However, mutation analysis can be used to identify whether or not an individual is CRIM positive or CRIM negative. It's important to note that about a quarter of CRIM positive individuals can develop antibodies to replacement therapy. However, this antibody production usually isn't significant as the completely neutralizing antibodies that are developed among those who are CRIM negative. Let's talk about newborn screening. Newborn screening is based on GAA enzyme activity, measured in dried blood spots. The current methods that are in place right now are not based on measuring the total amount of protein that is there, but actually measuring the enzyme acidity. Three general ways that can be done. Fluorometric assay, that is what is used in Taiwan, that we will talk about later. GAA enzyme activity level can also be measured through mass spectrometry. There is a preliminary step before the sample is run through mass spectroscopy. And third is digital microfluidic, really

based on the fluorometric assay, but these are the so-called labs on a chip, and a different technology is used. Again, I really want to emphasize that all available screening tests are based on measuring enzyme activity and the methods that are in place to effectively measure that enzyme activity. There is no data available right now about whether any of these particular screening strategies would operate better in a high-throughput setting such as in a newborn screening program laboratory. There is work that is addressing the relative merits of the different screening technologies that is underway and being conducted by Dr.[inaudible] and I would expect that those results will be available in about a year. The diagnosis is based on establishing the low functional GAA enzyme level and then by genotyping. Genotyping does four things. First, I can rule out pseudodeficiency. It can identify carriers, they can predict whether or not the individuals can have the infantile-onset form versus late onset. Again, if it is not infantile onset, it is hard to predict exactly when the symptoms for late onset—those affected by late onset Pompe Disease—will develop symptoms. And the final thing that genotyping can do for you is a can predict CRIM status. As we have been told, genotyping can be completed in about two days, and there are several laboratories that are doing that right now. Just to summarize this slide, if an individual goes through newborn screening, and whatever the screening algorithm is that is being used ultimately is a positive screen, than the next step would be to get blood from that baby to both confirm that the GAA enzyme activity level is low, and also to genotyping for the reasons described on the slide.

Let's talk about enzyme replacement therapy. In some replacement therapy, it was developed to replace the GAA deficiency. There are two drugs that are approved for treating Pompe disease and manufactured by Genzyme. They have slightly different indications and I have listed out there the wholesale acquisition costs for each 50 milligrams vial. The key things to remember about the enzyme replacement therapy is not -- affected individuals typically require infusion every two weeks with central line. They typically receive 20 milligrams per kilogram and it takes about two hours to deliver the enzyme replacement therapy. Sometimes based on the clinical condition or whether or not antibodies have been developed, the infusion dose could be changed. In terms of adverse effects, there have been described infusion associated reactions, mild allergic reactions. And I'm not going to talk about that any further; those are described in the evidence report. The more important consideration is the issue of antibody formation, especially in those patients who are CRIM negative. In the report that we sent out, you can see the details of the evidence review. As is typical of our work, they are divided by key questions. We get extensive input from a technical expert panel, for which we are tremendously grateful to those individuals spending time to help us understand the issues as we do the review. There are a total of 73 different reports that were included in the review. And as we were working on the review, we have a series of interviews, both to make sure that we understood fully the material that was in the reports and also to look for important unpublished data. As with any rare disorder where knowledge is rapidly being generated, looking for sources of unpublished data and talking to the experts in the field really helps us put this into appropriate context. Again, I would like to thank those people who have spent their time to help us understand what the key issues are. On the slide, I list the expert panel members and the technical expert panels that we helped. A total of five of them, three of them focused on the decision analysis on the review, and we typically have between three and four

people on each of those panels. Without belaboring the point, it was tremendously interesting and tremendously valuable to us. In addition, on the next slide, we have a list of the expert panels that we had separate interviews, as well as the dates when we contacted them, and again I would like to thank them publicly for coming.

What I'm going to do is summarize the evidence report from the 3000-foot level. The key details are in the report itself, but for the purposes of this talk I will make sure that we don't get too lost in the details ,so we can really focus on the issues that are important. In terms of the expected epidemiology in the United States, from our review, we would say that the overall incidence is about one in 28,000. I will talk in a second about where that figure comes from. It is somewhat different than the one in 40,000 figure that is often cited, for the one in 40,000 was done in the late 1990s with the relatively small number of samples. And so I think that the more recent studies are much more informative in terms of what we would expect about the overall incidence. Looking into the large categories we spoke about before, there's infantile-onset disease, which pooling our estimates, we believe it affects about 28% of those with Pompe disease. Again, to repeat that, 20% of cases of Pompe disease are infantile-onset. Of those, about 85% are classic Pompe disease. Those are the patients who present with cardiomyopathy and 15% would be the non- classic Pompe disease. Among those cases of classic infantile-onset Pompe disease, about 75% our CRIM positive or, to put it another way, 25% are CRIM negative. The other category is late onset disease, and based on pooled estimates we estimate that about 72% of cases of Pompe disease are late onset. We also estimate, based on data that I was shown, that pseudodeficiency in the United dates occurs in less than 1% of births. Again, these are summary estimates across the United States. If you're in a state that has a high population of East Asians, one might expect pseudodeficiency to be higher. Let's talk about where that figure that I presented to the overall incidence confirmed. A study that was done in the University of Washington, led by Dr. Ron Scott, that was based on anonymous dried blood-spots. The screening, nobody can see this out there, but I'm using airflows from screening because these were anonymous dried blood-spots. There is no clinical correlation or any sort of follow-up with the babies from which these blood spots came from. It's not entirely right to say that it's a screenings study, but one can imagine it was a screening study in that the samples that had abnormally low levels of GAA enzyme activity were genotyped. From those almost 112,000 samples, there were four that were consistent with late onset Pompe disease four that were consistent coming from carriers, three that were consistent with carriers of one pseudodeficiency allele and six were consistent with heterozygous for pseudodeficiency. If you take the numbers that are in the report by Dr. Scott, you can estimate an overall incidence of about one in 27,800. I want to remind everyone that this is the anonymous dried blood-spots study. It's not the same as screening, but because they did the genotyping I think it's fair to look at the overall number of cases that would be expected to have Pompe disease.

The overall positive rate from the screening process was .015%. Real screening study in which babies were followed up them .015% of the babies we need to have diagnosed -- for a blood sample for GAA enzyme activity levels estimate and genotyping. The overall positive predictive value based on genotype only was 24% across all types of Pompe disease. In the study, no cases of infantile Pompe disease were identified. Next slide. So as I think everyone knows, Missouri

began screening on January 15 of this year. The data in the report are replicated here. This is through April 29, 2013. There were 25,000 -- samples. Of those one case was likely classic infantile-onset disease, one case of non- classic infantile-onset, one case a late onset Pompe disease, to carriers, one case of pseudodeficiency and three false positives. If you calculate the overall incidence of Pompe disease, regardless of type, that is one in 8657. The overall positive rate, the proportion of babies that needed to have diagnostic follow up, was .03%, and overall positive predictive value of 33%. So the question that comes up, of course, is why is the overall incidence so much higher from this population of newborns? And I would just caution people to remember that this is a screening activity that has just started, and it's relatively small numbers. And so the denominator may change however, and I owe a debt of gratitude to the folks in Missouri because they send me the -- they just sent me the updated numbers so as of May 15. This is four months into screening, they have tested 7724 samples and they have just had two more positive screenings. I have no further information about those positive screens. Next slide please. I would next like to talk about the Taiwan newborn screening program. They use a fluorometric assay. From their most recent report they have tested nearly 474,000 samples, from which they have described nine cases of infantile-onset Pompe disease, 26 cases of later onset Pompe disease, and let me be clear, they use a slightly different terminology then we use in that the later onset includes the non- classic infantile form and the late onset form. We can talk later about why there is the slightly different terminology, but I don't think it really significantly changes the evidence I'm going to be talking about now. One of the key things to notice if you read the many reports that of come out of the Taiwan newborn screening activity is that they change the algorithm over time. When it was first begun, there's a concern that they did not want to miss any cases, and so the threshold for having a positive screen, which was much lower than it is now. Because they have a higher proportion of individuals with pseudodeficiency there, their false positive rate was higher. Now they have a two-tiered approach. And that is what I have described below. And because they have felt this two-tiered approach, they are able to go back and model what would've happened if they were using that two-tiered approach all along. And what I can tell you is that they would not have missed any cases of the infantile-onset disease and they would have detected 24 of the 26 cases of later onset disease. If you look across the Taiwan experience, their overall incidence of all forms of Pompe disease is one in 16,919. Their overall positive rate, and this is from the revised algorithm, is .053%, and they have a very high positive predictive value in excess of 90%. Next slide please.

This slide summarizes the three screening activities that I described. Again, please remember that the study I described, out of University of Washington, is screening in the sense that there is follow-up with babies -- based on anonymous dried blood-spots. But what I would like to highlight is they all used different approaches, mass spectrometry, digital forensics and the incidence varied somewhat from the one in 27,000 that the University of Washington -- one in 8607 in Missouri and one and 16,919 and Taiwan and you can see the overall positive rate that is listed here. This is not the same as doing a direct comparison across all methods like the work that Dr. [Indiscernible] is leading right now. I did think that showing this side-by-side might give you some insight into these different screening tests. Next slide. What I would like to do now is talk about the impact of enzyme replacement therapy. This first slide is just to summarize the

clinical course before enzyme replacement therapy based on historical data. The mean symptom -- I should say the median symptom onset for infantile would be -- historically when the babies were diagnosed is two months of age. And you'll see that we have, with and without cardiomyopathy below, so the numbers don't exactly average out to the median there and that's because we pulled these from different studies. But what I hope it does is give you a sense that babies with infantile onset disease are typically picked up around -- or develop symptoms from the second month of life. But diagnosis can take some time, and you can see the median age of diagnosis for infantile-onset overall being 4.7 months. They can be a lot longer for those with cardiomyopathy. For those with infantile-onset, the median age which a baby is required for mechanical ventilation was 5.9 months and that was for 29% of the babies, and the median age of death was 8.7 months. And you can see in the final columns, the percentage of ventilator-free survival across infantile-onset, from 12 months through 24 months, is about 26% and 12 months down to 9% ventilator-free survival at two years of age. Next slide. This is a slide laying out what we know historically and again, this is from the Pompe disease registry around symptom onset diagnosis, death and survival for those with late onset disease. The median age of symptom onset, that is when individuals begin to seek consultation, having a problem, was 28 years of age, but you can see it's another 10 years before diagnosis is made, and death can be 27 years later. And if you look in the final column I show the estimated survival post-diagnosis from five years through 30 years of life. Again, one of the things I want to emphasize is that there's a broad spectrum of late onset Pompe disease, and I will show some more information about that in a bit. Next slide. There been several studies looking at the effectiveness of enzyme replacement therapy. The first I would like to summarize is enzyme replacement therapy compared to historical control enzyme replacement therapy, 52 weeks out from the first infusion given by six months of age reduced the risk of death by 95% to reduce the risk of death or ventilation by 87%. The overall survival is 36 months, was 72% in the overall ventilator-free survival at 36 months was 49%. This is one of the earlier studies of the effectiveness of enzyme replacement therapy, and a couple of things that likely affected the survival. First, in this early study, those who were CRIM negative had significantly worse outcomes. At least through four of the 18 subjects in the study were CRIM negative, and this was done before the new immunotherapy techniques I will be describing were developed. The other thing is that there is lower survival, if enzyme replacement therapy was begun, after six months of age. There's some evidence from this work that earlier intervention is better. I will show some more of that in a bit. Next slide.

These data come from the Pompe disease registry. Genzyme, which manages the Pompe disease registry, did the analysis for us. I would point out that these data are not adjusted for any potential confounders or factors related to the baby. These are just the crude unadjusted numbers. Our question was, how does survival and mechanical ventilation-free survival vary, if you begin enzyme replacement before three months of age or at three months of age or later. From this, we excluded the patients that were identified in Taiwan because we wanted to get a sense of those babies that were detected clinically. How do things vary by early initiation of enzyme replacement therapy versus later? And you can see that for survival, there is a suggestion that there is approval and survival at two or three years of life—when enzyme replacement therapy is begun earlier rather than later. And the same difference appears for --

mechanical ventilation-free survival. If you include the babies that were detected in Taiwan, survival in mechanical ventilation-free survival is even better, and that is because the babies that were detected through newborn screening in Taiwan are also still alive. Next slide please. Let's drill down a little bit more into the Taiwan experience, and think a little bit more about the benefit of screening and early initiation of treatment. Nobody's going to be surprised if there are no randomized trials for screening. Looking at the Taiwan experience is critically important. What we know is that newborn screening leads to significant earlier diagnosis, and first 22 days versus 36 months in Taiwan. These numbers are relatively small. So, here five babies detected through screening and nine babies that were clinically detected. But you can see that at 24 months, there was 100% survival, of ventilator-free survival, versus those only detected, 89% survival and 67% ventilator-free survival at two years. What I have done here is reproduce a slide from one of the reports from Taiwan that shows the survival curve, the one on the left is the proportion of raw survival and the one of the right is the mechanical ventilation-free survival. The line that has the really steep drop-off is the historical data prior to the availability of enzyme replacement therapy. That is a historical story. And you can see that those babies who begin treatment earlier than five months of life were similar to those babies that were detected through newborn screening, and doing much better than the babies that were detected and begin treatment later. Next slide.

I will leave this here for a second so you can take in the survival curves. I think everybody in my room is nodding their head, so I feel safe to go to the next slide. One of the issues that has come up and that we explored was the issue of antibodies to enzyme replacement therapy. As I described before, all CRIM negative patients, and about 25% of patients that are positive, can develop antibodies—that is, the antibody production in those who are negative that is associated with a poor outcome. That's where you develop the neutralizing antibodies, remember that all patients who are CRIM negative have classic infantile-onset disease and will require enzyme replacement therapy. Assuming that the baby doesn't die before they get identified, they are going to get enzyme replacement therapy. The issue is that screening is going to treat these babies, who are CRIM negative with infantile-onset disease, earlier versus later. So, screening moves to the earlier initiation of the enzyme replacement therapy. What has been described now is immunotherapy, administered in early infancy, can protect against the development of neutralizing bodies. Based on the small case study that suggests that immunomodulation after the initiation of enzyme replacement therapy is not as effective in protecting against the development of neutralizing antibodies. I mentioned at the beginning of this talk that I was going to present some things that weren't in the report that you received two weeks ago. This is a manuscript that was recently accepted for publication by Dr.[Indiscernable] group where they described seven CRIM negative subjects who received modulation around the time of enzyme replacement therapy. And they have not developed antibodies, and their ages are 20, 21 months, 26 months and 29 months. They required a second course of a immunomodulation with Indiscernible] and methotrexate as well as IVIG. primarily to offset and help prevent infection. Those two children required an effective course of immunomodulation work, 29 months and 20 months of age, and one who died from respiratory failure at age 15 months. Now let's talk about the issue of late onset Pompe disease.

There are no trials of presymptomatic enzyme replacement therapy for late onset. And in general, treatment decisions are based on the presence of clinical findings such as this or muscle damage based on biomarkers such as elevated CK. However, a MRI can also be used to show muscle damage. Right now the recommendations for how frequently to follow-up or what to get for individuals with late onset disease is not standardized. I think it's important to consider some of the potential harms of early identification, which includes treatment with enzyme replacement therapy at a time when they don't need it. Central line placement, the economic cost of lifeline treatment and psychosocial harm; for example, finding out that your baby has Pompe disease and not knowing when symptoms might develop. And if it is not for a long time, that harm might transfer to the affected individual. However, there is evidence from a randomized trial that enzyme replacement therapy for symptomatic individuals, individuals in their 40s, that enzyme replacement therapy can improve respiratory status and motor function with the late onset therapy study. Next slide please. But I think one of the key things to consider is that the affected treatment, begun after symptom development, might be limited because the muscle damage is irreversible. Enzyme replacement therapy won't restore muscle tissue that is lost. And it's biologically possible that treatment begun before symptom development might avoid that muscle damage. Again, just to repeat what I said, the muscle damage can't be reversed by enzyme replacement therapy, and there are some MRI studies that show even in individuals with very minimal weakness, they are to have muscle damage that is beyond what one might expect if we're looking at the MRI. And there's also these autophagic bodies within muscles that persist after enzyme replacement therapy, even after the reduction of the glycogen in muscle cells from the enzyme replacement therapy, which indicates that there may be some muscle damage that is not reversible—that had they known about it at that time you could have treated it and perhaps prevented the development of these inclusion bodies. The only way to know this would be to test this hypothesis, and require prospective study and it's clear that such a study would take many years both to accrue sufficient number of patients but also to monitor for differences in muscle damage. Next slide. I mentioned before I was going to talk about some of the range of symptom developments in late onset Pompe disease. There is a key series from Taiwan that identify six patients with later onset Pompe disease, asymptomatic at diagnosis, and four of these we would classify as late onset. There was a child 14 months of age, who had hypotonia, 34 months of age with frequent falling, 36 months of age that also had frequent falling. And there was a seven -year-old who was diagnosed, through identified siblings through screening, who had hypotonia—individuals that would not have come to medical attention but clearly had some signs of weakness. Let me summarize the evidence review so far. And that I'm going to hand the virtual microphone over to my colleague, Dr. Prosser. First, when you do screening, it identifies all forms of Pompe disease. You can target -- just for the infantile form. Pseudodeficiency is less common in the United States than East Asia, and so presumably for screening. We won't have the same issues related to false positives due to pseudo immunodeficiency. The third point is early identification of infantile onset, clinical detection, can improve outcomes. Most cases of infantile onset disease are in CRIM+ — CRIM negative is associated with worse outcomes but immunotherapy appears to improve outcomes, and also from the case years I described before it seems like early immunomodulation may be more effective than later immunomodulation. Next, most cases of Pompe disease identifying through -- late onset form. As I described before,

epidemiology and then finally, there is no direct evidence that presymptomatic treatments of late onset Pompe disease leads to better outcomes. However, there is biologic possibility that that is the case. With that, I would like to invite Dr. Prosser to describe her work associated population levels benefits using physician analysis. But before Dr. Prosser begins I would like to remind everyone that the results of the decision analysis that you're going to hear are not in the report that you received two weeks ago and part of that is caused there was some very important data that we were able to get from the Pompe disease registry that we wanted to incorporate into this model to really get a full and complete understanding of what might be expected through screening. Dr. Prosser?

Thank you Alex, good morning everyone. And the next few slides I will be going through the decision analysis component of the condition review to assess population-level health benefits. For the condition, I will start with a little bit of background about decision analysis. And general decision analytic modeling is a validated approach for evidence and used by other decision-making bodies, such as the U.S. preventative services task force, and can be used as an alternative or complement to traditional analysis and it's particularly useful in situations in which there is little public evidence available, which is clearly the situation for most of the newborn screening conditions that are being considered. The main objective in the condition review is to use simulation modeling to project population-level health benefits, in particular, to establish some ranges for population health and if it's are expected to be given the level of evidence that we have right now. This approach can also allow for the explicit identification of assumptions, which can also be informative and helpful to the committee in their decision-making. And we can also identify key areas of uncertainty which can be used in planning for future research. We developed a computer simulation model to evaluate outcomes for universal newborn screening for Pompe compared with clinical identification. The simulation modeling uses input data that was collected during the evidence review, primary data that was available to us through the evidence review and shared through the Pompe registry and also by expert panelists that are doing research in this area as well as public data, supplemented by information provided by the expert panel. We helped three expert panels which were critical to the development of this model—in December, January, in April. During these expert panels, we reviewed the structure of the model and reviewed the assumptions that were being used to guide transitions within the model, and also identified available sources of data input that had not been previously identified. We determined that the three key health endpoints that would be included in the simulation model for a number of cases identified and subtypes within that. The number of deaths averted and the number of ventilator dependent cases averted. This last endpoint is typically reported in the literature, as ventilation-free survival, we reported here as ventilator-dependent cases in order to make it a separate endpoint from death. Some of the key modeling assumptions are listed on the slide here. In particular, all identify cases of infantile-onset Pompe disease that would be eligible for ERT, where modeling key outcomes for infantile-onset cases only. That assumptions and the expectations of the benefits and potential harm of newborn screening relating to late onset cases is addressed elsewhere in the review. In particular that's because the additional number of late onset cases that will be identified with screening is somewhat unknown at this point.

Assuming an annual US newborn cohort of 4 million newborns, and this is assuming that these are newborns that are not at increased risk for Pompe disease. Identical hypothetical cohorts, through the screening and clinical identification submodels, to evaluate the potential outcomes for screening compared with clinical identification. We project that under screening, 134 cases on average will be identified each year. And that of these, 40 cases would be expected to be infantile-onset and 94 cases would be expected to be late onset. Dr. Kemper addressed some of the uncertainties related to this and point earlier in the presentation, at the clinical prevalence of Pompe and the absence of screening is not well-defined. This may be anywhere from 40% to 70% of these cases may be undetected in the absence of screening. We would also expect approximately 10 false negative results and anticipate those would be late onset cases only. I am not -- not shown on the slide but we also have a projection for screening outcomes within the model and there would be approximately 130 false positives expected per year. This is based on the Taiwan algorithm and they differ depending on the actual algorithm that was implemented by specific states. This slide shows the breakdown of the number of cases identified or infantile-onset cases only. The middle column shows the results for newborn screening and the right-hand column clinical identification. We would anticipate the identification, on average, of 40 cases of infantile-onset compared with 36 cases of infantile-onset under -- identification ranging from 19 to 61 for newborn screening and 16256 for clinical identification. Within the 40 cases identified under newborn screening, it's anticipated approximately 85% of 34 cases would be infantile-onset with cardiomyopathy. And six cases would be infantile-onset without cardiomyopathy. Under clinical identification, it's anticipated that the same number of cases of infantile-onset with cardiomyopathy would be identified, but at a later time of identification then a newborn screening. And so the model includes the health benefits associated with that earlier identification and initiation of treatment under newborn screening. Infantile onset without cardiomyopathy, the expectation is that an additional four cases would be identified within the first 12 months of life compared with clinical identification. So, the health benefits of the two cases would reflect earlier identification treatment and 44 cases that would be likely undetected under clinical identification—the model evaluates the benefits of those events that would otherwise be at higher risk for mortality and ventilator dependence.

In terms of the results, the benefits of newborn screening for infantile-onset was due to the earlier identification and initiation of treatment, approximately 22 days for newborn screening compared to four to five months on average, although there is variability around that distribution. For infantile-onset without cardiomyopathy, again the main benefit there is the identification and treatment of four additional cases that would likely be missed until later and potentially much later in the absence of newborn screening. The key health outcomes, and this is screening, would be approximately 13 averted deaths for infantile-onset with a range from eight to 19, of those because infantile-onset with cardiomyopathy are at much higher risk of mortality and morbidity than the infantile-onset cases without cardiomyopathy, 12 of those averted deaths would infantile-onset with cardiomyopathy and about one on average the infantile-onset without cardiomyopathy. In addition, our other key health outcomes was that there would be 26 additional individuals who would not require invasive ventilation. And I should clarify that these are 36 months, using the best data available at this time. In summary,

their projected health benefits for identified cases, we are projecting these identified health benefits for infantile-onset only. The benefits are both in terms of increased survival as well as fewer individuals that would require invasive ventilation. The benefits of identifying late onset cases are not included in the decision analytic simulation modeling component of the review. We do have the additional details of all the input parameters and functions that were included in an appendix, to be evidence reviewed, that either has been or will be distributed to the committee. And includes a model schematic, with all the details underlying the model, and also looking forward to answering any questions at the end of the presentation. I will turn it back over to Dr. Kemper. Thank you.

Thank you very much, Dr. Prosser, for the excellent presentation and finally, the third presentation will be by Jelili Ojodu on his results of the assessments of the capability of newborn screening, including programs to implement comprehensive screening for Pompe disease.

Thank you Alex, and good morning everyone. Can you hear me?

Yes we can.

Lovely. This morning I will be presenting not my work, but the work of a collective group of individuals from state newborn screening programs. Just a reminder, 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 a public health impact assessment complement as part of the evidence-based review for new conditions that are being considered for the Recommended Uniform Screening Panel, also known as the RUSP. In order to address this new requirement, a public health impact assessment was conducted to evaluate state readiness of the ability to add conditions. Specifically in this case, as I will be describing over the next several slides, to add Pompe disease to the panel of disorders. I'm going to talk a little bit about the criteria for selection of the states that we included on the survey. We did not survey every state for many reasons. The states that we primarily surveyed had the general characteristics or criteria for [Indiscernible] that is noted on the slide above. We wanted to make sure that we got representation from each collaborative. We broke down each state into population sizes so less than 50,000, 50,000 to 150,000, births per year and then over 150,000 births. If a state had a mandate to add a condition once it is added by the Secretary's Advisory Committee, every state outsources their newborn screening program or does it in state. A second screening requirement—as you know, about 20% of the babies born in the United States have just received two screenings. The screening conditions of interest, equipment on-site, and these are specific conditions -- specific newborn screening condition factors, and then the experience of screening for similar conditions. And so with this list of criteria for selection, we selected examples -- a sample size of a total of 13 states and I will read off their names. The states of Massachusetts, Delaware, New Jersey, South Carolina, Illinois, Minnesota, Missouri, Iowa, Nebraska, Texas, New Mexico, Oregon, and Washington. As I noted earlier, the criteria for selection is represented on the slide, whether it is the regional collaborative, the state mandate to include a condition if it's recommended by the Secretary's Advisory Committee. If they

outsource their newborn screening testing. Population size, and we also consider the academic affiliation, if a state newborn screening program has an affiliation with a university or an academic institution. And finally, we added a couple of other states that are in the process of actually screening for Pompe at the moment, or have a pilot to screen for Pompe.

The survey was done in two phases, first was electronic, and this was over several months. We conducted this electronic survey to get a sense of what the public health impact of adding Pompe -- readiness of the ability to state newborn screening programs by these survey of questions that was sent to all of the states, 13 in total. As of today, we actually did get every state to respond to the survey. Although prior to putting the slides together for this presentation, 12 of the 13 states information is what will be presented to as part of this presentation. The second stage, after we collected the electronic survey from the state, was to do an in-depth phone interview. It lasted about an hour. Some cases it took longer, with the individuals from the newborn screening programs, which included for the most part the state newborn screening lab director and in some cases follow-up coordinators or managers in general. To get an in-depth analysis or in-depth thought process on some of the questions that they answered, so we can better give a collective overview of state readiness and feasibility as it relates to the Pompe screening. For the purposes of this presentation and this project that we embarked on, we did define feasibility in the following way. For those program directors, newborn screening program directors that responded, feasibility in the sense -- it was in the form of a question, and the question was did the newborn screening directors believe that there was an established screening test? A clear approach to diagnostic confirmation? A clear approach to long-term follow-up? For the purposes of readiness for this project, the question that we asked the state, as it relates to readiness, was do the program directors feel like they have all of the resources needed for screening, diagnostic confirmation, and long-term follow-up? And then most important of all, as it relates to readiness, and you'll hear me talk about this a little bit more in detail, the authorization to screen in their individual states.

I have to think a list before putting the slide together because this is a really good representation of the kind of information that we got as a collective from the states that responded. The general process of adding the condition in a state goes to renumber processes as listed on the slide here. In some states, they will consider if a condition has been added by the Secretary's Advisory Committee or added to the Recommended Uniform Screening Panel. And to the left, you can see all of those factors. To the right of the slide is how long it takes, and all of these factors can be done simultaneously. However, it does take time. The state has to decide whether or not to add that condition, after it has been added or not by the Secretary's Advisory Committee, and I should also note here that there are some states that are ahead of the curve that will add a condition regardless of whether it has been added by the Secretary's advisory committee. We know there are some states that screen for conditions that are not on the Recommended Uniform Screening Panel. This wasn't the only criteria for selection here. In some states, they have to change the rule or statutes related to newborn screening to add a new condition to their state uniform screening panel. Obtaining funds. Depending upon the methodology, they laboratory equipment needed, the staffing that is needed, all of these things have to be considered and in fact, there are some states that actually require a cost analysis of

the new condition being added to their state newborn screening panel. Before that condition is added, and then, the state will in most cases, conduct an implementation or pilot phase of adding this new condition to their state newborn screening panel. This includes everything from the validation of the test methodologies, providing educational materials, to all of the newborn screening systems, including the clinicians, and other activities related to implementation

---

And reference to -- these are pretty match aggregated collective information that we have signed up into one slide here. Factors for implementation for new conditions to every state's newborn screening panel, number one factor, to add a condition for implementation is that the authorization to actually screen for that condition in a state newborn screening program. Once that decision is made, then the other bullets here that I noted whether it's the securing of funding, contract for equipment and reagents, depending upon the methodologies and the number of additional equipment that is needed the organization of space, validating the method, and I'm going to note this now and I will note it again, the only state that is currently-- that currently is screening and has a mandate to screen for Pompe is still in the process of validating their method to screen. They will be done with their validation in July of 2014. Getting material, having new staff, training, education, updating reports, updating IT systems. These things take approximately, as noted on the previous slide, between -- from the minute that they get the authority to screen to the point where they are actually implemented screening anywhere between one to two years, depending on the state. I would like to know the stakeholders involved in adding a new condition, to anyone on these panels. It includes, among others, the advisory committee. This is state specific. It can be different from state to state but overall, in general, the stakeholders involved in adding a new condition include advisory committees, consumers, state health officials, legislators, if your state requires you to change the statutes, then definitely the legislators are involved in that process. In some states it'd be the state board of health, public health department, and I cannot underscore the role of advocacy groups whether it is condition-specific group and the addition of new conditions to state newborn screening. Programs panel. Over the next couple of -- more than a couple, several slides, I will be talking briefly about the key findings from the survey. Remember the focus of this is on the feasibility and the readiness of state newborn screening programs to add and screen for Pompe. I think as noted by Dr. Kemper and Dr. Prosser, there is no definitive method, at least as it relates to the best way to screen for Pompe, whether choosing any one of the three methods that Alex noted earlier. We know that the folks -- [Indiscernible] is working on an analysis on the different methodologies here. But as of today, as noted by screening programs, there is no definitive method in the best way to screen for Pompe in a population newborn screening setting right now. 55%, or six out of 11 of the program directors surveyed, were very comfortable with their newborn screening programs ability to provide diagnostic confirmation for Pompe disease. While 45%, or five out of 11 of them, were uncertain, eight out of 11 of the program directors surveyed were very comfortable with their programs ability to provide/facilitate treatment as it relates to Pompe. 64%, or seven of 11 of the newborn screening program directors, felt they were comfortable with their programs ability to conduct follow-up services for Pompe. I should note as part of the comments that we got in aggregate from some of the states and as noted by Dr. Kemper, that we are -- state newborn screening programs still need to develop a follow-up method and procedures as it relates to the late

onset of the condition before they start screening for. That will be very important moving forward. 83% and it changes here for a number of reasons, as I noted by the time we completed or concluded our survey, we did not get the responses from one of the 13 states. And then there is one state that is already screening for Pompe disease right now, so they did not respond to some of the questions. But 83%, or 10 out of the 13 states surveyed, rely upon their newborn screening advisory committee and the state health official to assign or assist with adding a new condition to their states panel. 73%, or eight out of 11 of the newborn screening program directors that were surveyed, did not have adequate funding if they were required to implement screening for Pompe disease today. Again, this goes back to the previous slide that I showed earlier. On the authority to screen, or the process of adding a new condition to each state score panel. What they have to go through prior to adding that condition. It's important to note that at least about 50% of the state, or seven out of 11, require a change in their states rule or statute to add a new condition to their own states panel. Five out of 12 states require legislative action to add a new condition to the panel in their state.

As it relates to readiness, one of the main factors that came up from the collective aggregate information was staffing, and the need for adequate staffing of the newborn screening program and adding a new condition to each state's core panel of disorders. 73%, or eight of the 11, believe that if they were required or if they want to add Pompe disease, they would not have adequate staff. 55%, or six of 11 of the program directors, reported historical difficulties in recruiting adequate staff with the necessary expertise. And I think some of this is definitely from the formation [Indiscernable] of condition that was added to the uniform screening panel and that it was a molecular test. There is a need for molecular training, education, staff, space, in the laboratory setting and then beyond into the broader newborn screening system before the states were able to add it to their core panel of disorders. 73% of the states, still following up on the key findings for readiness, 73% of the states -- the program directors surveyed, or eight of 11 noted, that there were a shortage of metabolic specialists or those trained to handle the cases of Pompe in their individual states. This certainly is some -- a concern that needs to be addressed before each individual state will add Pompe into their core panel of disorders. And then there was collective aggregate -- on the short-term follow-up programs, we will need to develop additional protocols to educate hospitals, providers, on what to do with out-of-range results. And I think this is my last slide here in reference to key findings. Before I summarize briefly here, there were a number of states, several states, that had noted that they have not been able to secure funding to conduct newborn screening for prior conditions that have already been added to the core panel of the Recommended Uniform Screening Panel. Of the states we surveyed, only three of them, three out of the 13, have currently added Severe Combined Immunodeficiency's as part of their individual state's uniform screening panel.

In summary, I would like to thank all of these states newborn screening programs for all of the input that I'm able to provide to you all on the advisory committee today. The newborn screening processes, as it relates to validating the different methodologies and platforms related to population screening for Pompe, is still underway. And as I noted earlier, it takes time for individual states to validate their methods of testing. Before they actually start the mandate or implementation of screening in their states, there is uncertainty as it relates to the

diagnostic follow-up or treatment, especially for the late onset of Pompe and the need to develop more educational materials. Since this screening for Pompe is in newborn screening settings, newborn screening population setting will be a paradigm shift. As you know, for most not all the conditions that we screen for, the infants that are identified with the early-onset of the condition, and so this is something that needs to be addressed individually in state newborn screening programs prior to adding that condition to their own core panel. And I think that's it.

Thank you very much. This completes the presentation from the physician workgroup and I will hand a virtual baton to Dr. Bocchini.

Thank you. And thank you for the presentations, which relate the main points that were developed by the condition review workgroup. Thank you all for your efforts and for the concise and clear presentations. I would like the three presenters to have their lines left open, and I would like to open the lines of the committee members and organizational representatives, so we can start the discussion questions and comments related to this review presentation. Operator, if you open the lines, for the committee members and organizational representatives.

All lines are open.

Please note that I will ask committee members to have the opportunity to speak first, and then once committee members have completed their questions and comments than we will ask the organization representatives to follow. Again, when speaking, state your name each time to ensure proper recording and for the public, you too can ask a question, if you go to the lower portion of the chat box on your screen you can type in your question and click the send icon. It looks like a small balloon. And we will be able to have the people from the condition review workgroup answer those questions. I would also like to acknowledge that [Indiscernible] did join the morning session following the roll call. This now is open for discussion, questions and comments from the committee.

This is Fred Lorey, if I could jump in.

Yes Fred.

Hi, thanks. Before I make comments, I want to thank Alex and his group for an excellent review. I know that was a lot of hard work. I also want to thank the family members, and patients and representatives of Pompe disease, and also Jelili Ojodu for providing some public health impact to this. As you know, I am representing the only state program seat on the committee. I reached out to some of my colleagues over the last couple of days to get their input. And so all these comments come from several of us, and I will say we were remarkably consistent, I thought, in our responses. One thing that everybody commented on was we still feel a need for a large pilot before recommending Pompe. I realize a lot of data was presented on pilots, but I have a couple comments to make specifically on that. Some of the other comments are there was a statement -- one of the slides that was not necessarily curative. I am still not convinced

that the improvement in outcomes is really convincing. And, in a lot of cases, what was described as improvement in outcome with either not quantified or when it was, it didn't seem to be a particularly large improvement. And in particular, I think there was a slide on the early initiation of the ERT. I think the [Indiscernable] three months, and frankly those numbers didn't even look statistically significant to me. I don't know if those tests were performed on those numbers or not. Also, several of my colleagues stated that again, we are—with this particular disorder as with some of the previous ones—we are straying away from the basic criteria regarding treatment, outcome, etc.. And then there was the issue of the proportion of early-onset versus late onset. And it seems clear from all the studies that the overwhelming majority of cases picked up in newborn screening are late onset cases, which also one of the slides indicated are the ones we have no evidence that outcome has improved by early treatment. That is new. Looking at the pilot studies, I believe the Washington study -- I may have these mixed up. I think Washington found no early-onset cases. Missouri found only one. Everything else were carriers or late onset cases. Another comment, I think the prevalence rates we are seeing are somewhat misleading, but because they appear to be including everything they found, late onset, early-onset, I can tell, but considering the low number of early-onset cases detected, I am wondering about those prevalence rates. The last thing -- I wanted to say was on Jelili Ojodu's slides. Coming from the public health newborn screening programs perspective, many of the states make a statement that they are still not screening for SCID, and we know that to be the case, and recommendations came out in 2010, and still many states are not implementing it. It is the classic no-brainer newborn screening disorder without any of these concerns. These are my concerns, that we still haven't reached consensus on this meeting a newborn screening criteria, and some of the comments that the other state programs made as I discussed with them. Thanks very much.

Good morning Dr. Lorey. Thank you very much. There is much that you said in your comments that were related to decisions, so I will not address any of that but just to clarify a couple of things. One is the birth incidents or -- numbers, depending on how you like to think of it, those did not include pseudodeficiency or carriers, but included all forms of Pompe disease. So whether or not they identified infantile-onset versus late onset, we made that decision in terms of recording those numbers, because if you have been screened for Pompe disease there's no way to specifically screen just for the infantile versus the late onset form. I think in terms of the benefits of early intervention with enzyme replacement therapy, it's a hard story to tell because most of the reports about enzyme replacement therapy aren't in the larger case series, or if you wanted to think of the timeline experience from a population level court. Most of it comes from small case series or even case studies, which are -- they don't provide the denominator. It's a harder story to tell. But I think that in terms of the population level benefits, I think the best summary of it comes from the material that Dr. Prosser presented, and she was able to take the differences in survival data and run it through the analytic model, so it took into account from the cases you would find and so forth. I would just point back to that and maybe Dr. Prosser, if you want to comment on that in a second. And then my only other comment, and we had this debate in our group as well, as what constitutes a pilot study versus screening activity, and fortunately, our job is to just identify the data and report it. I would be interested to see here about how other people consider the Missouri experience. Again, it is not -- it is not our job to

make final decisions, but just to summarize what we have found. Do want to address the benefit of screening question and enzyme replacement therapy initiation?

Sure. First a clarification—on slide 22, which shows the outcomes among clinically detected cases, for ERT greater than or equal to three months from the Pompe registry—those are all data from clinically detected and treated patients. The left-hand side, less than three months, is not equivalent to the benefits of treatment with newborn screening. Those on the next slide, slide 23, which shows very small sample sizes, but the results from Taiwan for newborn screening and early treatment and a median age of 22 days. What we have done in the modeling is those results from the Pompe registry, we combine the data from less than three months and more than three months and the average age, that's where the number of each, four to five months for average initiation of treatment under clinically identified cases, comes from. Those two groups are combined, and then the comparison group for newborn screening is based on the data from Taiwan where at 36 months, there were no children that had died in that very small group of five newborn screened and treated, and they were also ventilator free at 36 months.

This is Don Bailey, complements for a very thorough and objective report. We appreciate all the work you did putting this business together, and also to the researchers and advocates who took the information from the last couple reviews and really have tried to provide better answers to the questions that we need to have answered. I wanted to ask a specific question about late onset Pompe, because obviously this will be the largest number of identified cases, and understand that there is no evidence yet on presymptomatic treatment for these individuals. But is there either a practice guideline, or some models, or suggested approaches for what you would do with those individuals in terms of follow-up. Focusing on surveillance, for example, how often should they use a physician? What should a physician be looking for? In terms of surveillance, of the timing and cycling with respect to genetic counseling and family support, helping families deal with this information over time, has anyone looked at that? Are there any guidelines out there for states or for practitioners to be following, in helping to support these children and families?

This is Alex again. Dr. Bailey, thank you very much for your kind words which we all appreciate. In terms of -- there are processes or guidelines that people use for following up individuals with late onset disease. Initially, there was follow up more frequently, some who said every three months, and then stretching out beyond there after early infancy if the child is doing well. And they are focused on looking for any signs of weakness or for signs of muscle inflammation, like using CK as a marker for muscle damage. There has been more recent work done with MRI, which can also show muscle damage earlier than you might see, with biomarkers and certainly before you would see weakness. The question really is when do you begin therapy? For example, that treatment would begin with the identification of either elevation of CK or the development of weakness, and certainly that is what is done in Taiwan. The real question I think is, given what we know in terms of the fact that enzyme replacement therapy doesn't restore muscle function, if you identify these babies through newborn screening that have late onset disease, should we be intervening even earlier? And to be honest, the only way -- and this

was the point I was trying to make, the only way that we will know, that is through some sort of approach to systematic case detection following those children overtime, and collecting data on them in a very organized and systematic way. And that would require research, prospective research. But your second question is around the role of genetic counseling, and whether or not that can reduce the potential harm. [Indiscernable] is not aware of anything related to Pompe disease so the best thing would have to do is make a [Indiscernible] from other conditions, which is outside the direct purview of the evidence review workgroup.

Great, thank you very much.

Thank you.

We did look a lot into the role of developmental delay, but because most of that was from [Indiscernible] and a little bit confusing, we left that in the report. But that was in response to your question at the last meeting, and I am happy to talk about that further if you would like.

Okay, thank you.

This is Coleen. I want to echo everyone else's comments about the evidence review. I really like the three components of it; it really helped me put a bigger or broader picture on it. I want to complement all of you that were involved in it. I had some specific questions that related back to Fred and Don's questions. This -- I'm not looking at a hard copy, so I may not have the exact rate on the screen. I think it is 22 and 2, the outcomes of early detection of classical infantile onset Pompe and from Taiwan, and then the graph from the paper. For some reason -- maybe I think of that 22 as being a bit misleading, and maybe you could help me with that graph and the paper. The dark line, the lines that go straight across, combine the newborn screening cases, those five cases. And then there's early medically evaluated, assuming they would have early treatment. Is that correct?

Yes.

There's really no difference between those.

Right. And then what is included in the table before that would be concluding both the early and the late together.

Exactly right. In some ways, that is perhaps over anticipating the impact. We didn't know how to have included that within the context of her decision analysis. I guess I was just trying to draw a little bit of attention to that. The fact that there's these are very small numbers, early treatment initiation, and newborn screening at least from this study, and I know there are lots of other data that was included, particularly the registry information. At least there -- I don't know if they have subsequent follow-up information that might help show how those two lines deviate. I wanted to ask if you knew anything more about that.

[Indiscernable] only knows the ones that were identified through screening are all still alive, and ventilator free. I don't know how old they are right now. And you are right, it's one of the things we were trying to tease apart. Because if you look at the individual case reports, in the very small case series when it's hard to generalize at what point does early intervention versus clinical detection really make a difference? Lisa, do want to comment?

That's a great question. Let me start by clarifying what we've used in the simulation model for the comparator for clinical identification. For the primary analysis for the 13 deaths, we used the combined data from the Pompe registry. And so what we haven't differentiated between is the two groups that were in the study less than three months, I think they have less than five months. Because from the perspective that we were using, we were evaluating for the total group of infant onset less than 12 months, it is not clear that we are not thinking about screening from the perspective of infant child onset, for only that very early group. But having said that, we did do a sensitivity analysis combined for the number of deaths, the lawyer pre-cases.

I am looking through the slides here.

I don't think that you have the appendix reports in front of you, but I will pull that up.

I do have it. Not the completed one, but the original one that we were sent.

What we have -- just to recap what we have for the combined group, would be 35% mortality at 36 months, assuming clinical diagnosis followed by treatment, and again that is for the average. We don't have it split out for early versus late.

Okay. And our assumption has to be that newborn -- will avoid any -- identification. And obviously the earlier the better but I am trying to --

---

The greatest benefit is for those cases that would have delayed identification and treatment, clearly there is not as much benefit, if you only look at cases that are identified less than three months or less than five months.

When Alex went through this, I didn't document the -- [Indiscernible] lines up there, the dark solid one and the light solid one, and the newborn screening and early identification. There's really no difference in terms of either survival or ventilator use at that time. We are not following -- [Indiscernible] 30 months or something like that? From 36 months, you know they have the -- no death and no ventilator use among the group.

Exactly. First of all, these are small numbers. And this issue of statistical differences makes the genealogist in me scream. The other thing, and this is hard to bring into the report again because the numbers are small, but it is also issues around difference in motor development. Here we are, essentially talking about ones and zeros. [Indiscernable] survival. But I also encouraged people to look at this, the case studies around development, because I think that's

the important part of the story, but one that is not mutually summarized because of the issues with denominators.

I agree, and just your sense beyond 36 months for those receiving earliest treatment possible. Newborn screening, give a sense of that? Select a [Indiscernable] or survival?

Both. Development for my reading of it didn't seem to have too much impact.

I think there is cognitive development, and then motor development and obviously social development, so if you set aside the issues of cognitive and social development, I think that it's hard to assess the babies that the young children that have significant motor development. It's really hard to assess their cognitive and social development. But my reading of the small case studies and small case series, is that those babies who do get into intervention early have better motor development

---

My reading as well, it was very complex.

It was complex to write and I apologize for that. I try my best, but you can turn and there are so many factors to be considered -- the degree of cardiomyopathy and other medications that -- receives. Does that answer your question?

Thank you.

One more quick question. This one has to do with late onset Pompe. On slide 26, where you said testing the hypothesis begun after before symptomatology, the require perspective suggestion of thoughts about looking at biomarkers you talk about.

I think if you look at the and you look at those, and I think that's at the end of the day he would have to do anyway, because it would take a time quality of life most important.

The distinctly non- that would not be clinically detected early and people who were identifying, but that assumes everyone is clinically detected early, and the data adducing clear that screening identifies you even earlier. So that is not a dispute. 22 days --

---

You get, enter into, significantly earlier and I can tell you get there were some babies who are clinically identified, they have pretty significant disease at the time they are clinically identified, so for reading the case study, some profound heart failure or similar unfortunate situation that gives rise to the identification versus the more planned approach to a child who might be asymptomatic at the time of detection. But again, it's hard to put denominator level information into that story. And, at least do you think that I captured that appropriately?

I think that's a good summary.

Could you explain to those of us who aren't familiar with the clinical context of Taiwan, the likelihood of being able to identify people earlier than a level of surveillance in population care compared to a larger distributed -- [Indiscernible] can you make any assessments?

If you're talking about the clinical detection --

Yes. How likely?

Obviously they have done a lot of work in Taiwan, people are more familiar with Pompe disease than they are in America. But it is still a rare disease, and it will be hard for me to imagine that the clinicians are that much different in terms of being able to pick it up. And again, if you look at the reports from Taiwan in those areas where screening wasn't occurring, it was still taking a couple of months or so until babies began to get into the diagnostic process and then around -- again, I'm not looking at the report of in front of me, so I may be a little bit off. For five months of age when they entered into treatment.

Thank you.

This is Dieter. I would also like to echo -- commend you for this excellent review. [Indiscernible] first I want to comment to Fred's comments. When it comes to the newborn screening criteria and how Pompe fits that or not, just considering a comparison to collect as EMEA or cystic fibrosis, I think Pompe works just as fine. The difference is the cost of treatment and then, what has come up several times, the time of when you should start treatment for the late onset cases which apparently you would identify primarily because there are more of those out there. Clearly we need some guidelines, as to figure that one out, and how to [Indiscernible] these patients. But I think that can be done. The other question I have is a general one as to -- it was mentioned at some point. What is an acceptable false positive rate? I don't know what that means. And finally, when it comes to the incidents, I don't know what is going on in Missouri, but it might be that they have relatively few numbers screened so far. Based on our study so far, we identified similar to Washington state, one in 25,000. With Pompe disease in the two we identified, in the first 50,000, would be considered to have late onset disease as well. I have no questions, just comments.

Let me thank you for your kind words, we really do appreciate that and I think you are right about Missouri in terms of the small numbers and be cautious about that. I think it's fair to say that the plan with Missouri is they gain experience with their screening and they will adjust the thresholds as well. You asked a question about the acceptable false positive rate as well, and I think that was directed more to Dr. Lorey than me. In my position, I don't have to tell you what is except able or not, just tell you what we found. I will dodge that bullet.

Are there additional questions from the committee?

Yes. Sorry, I am not on the committee.

But you are excited to ask your question.

No further questions from the committee I will go ahead to the organization representatives.

This is Fred. I have one more question. This is for Jelili Ojodu on one of your slides. I know you're not a mind reader so you may not be able to answer this, but maybe you had some additional comments from the phone interviews. I was a little perplexed by the slide that showed, on the one hand, something like 72% of the newborn screening directors felt comfortable with providing treatment or facilitating treatment. And then right below that was a lower number that felt comfortable with providing follow-up to diagnosis. That confuses me, because as we know newborn screening programs do not provide treatment. Was that question asked—provide or facilitate—or was it separated?

Slide 46.

Thank you. If it was not separated, as we know in order to get to treatment, we need to do the appropriate follow-up of this. Any thoughts on why the second number is lower than the first? It doesn't make sense to me, especially since the newborn screening programs do not provide treatment.

I'm looking at the question itself. I don't think it was separated, at reference to the treatment or to facilitate treatment. Now, remember when we sent these, we sent them to the newborn screening program to better understand what will occur in the newborn screening system. In other words, it wouldn't necessarily be common by the newborn screening lab director that we are hearing here. We would have hoped that they followed up with other newborn screening systems to get the answers as it relates to -- not just the testing but the treatment and long-term follow-up as it relates to Pompe. Why the difference? I am not sure. It's a slight one. Just one state that say that they have -- they are comfortable in there [Indiscernible] to provide or facilitate treatment.

Thanks for the explanation. I agree, you need the second one first to get to the first one. Maybe those questions in the future -- that distinction should be made, because providing and facilitating definitely from the program point of view, they are different things.

Right. And maybe Susan can talk a little bit, as one of the people they completed the survey.

Hi Fred, this is Susan [Indiscernible]. Can you hear me?

Yes I can.

Okay. As Jelili Ojodu was saying, I can't explain the difference in the numbers between the two questions, but when we looked at it from a system perspective, we looked at it as the availability of follow-up services. The availability of metabolic specialists throughout the state and what their current loads are. The ability of the current staffing of the program for the

immediate short-term follow-up piece. But also for the longer-term for diagnosis and treatment, the availability of specialty care within a reasonable distance. It wasn't just looking at the newborn screening program, but trying to relate it to the newborn screening system within Texas as we answered it.

Okay, thanks.

Additional questions from organizational representatives or comments?

This is Georgeanne Arnold representing the Society for Inherited Metabolic Disorders today. I have a couple of related questions. One is, how definitive is the cut off for effective versus unaffected update? When I look at the Missouri data, I suspect that it is just a blip from the sample size but it concerns me. I have some experience with another [Indiscernible] where we were finding a lot of gray zone enzymatic dimity, one known mutation and one novel variant. And a lot of people are in limbo about who is affected and who is not affected. I'm wondering how that has panned out in any of the programs that have done pilots, if people feel quite comfortable with calling effective versus unaffected.

This is Alex. That's a great question. It feels like a million years ago, I previously oversaw the development to the report on agencies, and that is an example of one where it was more challenging to establish the diagnosis. However, from all the reports we have read as well as talking to the experts, with genotyping one can definitively establish whether or not an individual is a carrier, pseudodeficient, has infantile or is going to be predicted to have late onset disease. The challenge is if you have late onset disease, the genotype can't predict when symptoms are going to develop and as I described before, there is a pretty broad spectrum of when symptoms might develop.

Okay.

This is Ed McCabe from March of Dimes, if I can follow-up on the question please. Just our experience in newborn screening—while the genotype phenotype correlation in Pompe is much tighter than in most other disorders, we know from experience with cystic fibrosis and others that when one goes out into the larger population in newborn screening, there's probably going to be variations even within the very tight genotype/phenotype correlation. I would just warn us that this one seems pretty tight, but I bet there will be unexpected phenotypes associated with genotypes.

Thank you for your comments.

This is Dieter. Just wanted to confirm what Dr. McCabe just said. In the case that we identified in our ongoing study, we encountered [Indiscernible] all the time.

This is Mike Watson with ACMG. I think I tend to agree with an earlier comment Dieter made about how this measures up with other things are ready for newborn screening, I have a couple

of questions related to how we are going to factor in the feasibility and readiness components of this. One I look at what was defined as feasibility, a lot of those are questions that seem to directly overlap what was done in the evidence review. I don't know whether aspects of that ought to be part of the evidence review, as they are an established screening test for incidents or an approach to diagnostic confirmation, and I can easily map the key questions approach that the evidence review takes, and how that might translate into the different levels or tiers of approval or disapproval. But it's a bit more difficult with the feasibility and readiness piece to get to what it really means, if it is a point in time assessment today of whether the staffing is available or not. So how those two components are going to be a factor together into a final decision or if there will be a decision made about the evidence review itself, and then a separate look at whether feasibility and readiness are the problem. If that turns out to be the case, how the committee impacts the financing or recommendations that might impact financing so the various entities that benefit from the prevention of a disease and the cost associated with management of affected people is not just the state. They probably believe, have a significant benefit financially through Medicaid and programs, but it is much more distributed I expect. That is one level of my questions. I wanted to comment on a previous question about balance. There are practice guidelines for Pompe disease that are fairly specific about what one does, and the diagnostic workup of an asymptomatic individual, presumably identified in a family, and what one does when they have identified the infantile forms and the periods following this, identified at six and 12 month intervals.

Thank you Mike for those comments. I think the issue about readiness will be after we have the evaluation of the evidence that has been presented to us, and utilize the matrix that we created, to include public health readiness in our decision-making process. So I think that will become more apparent as we get into that phase. And although there is an overlap, I think clearly there are specific issues that are associated with the feasibility that needed to be addressed on the public health side, but also came out in the evidence review. I think we will get more into that in the evaluation by the committee.

Any additional questions?

A genetic counselors clarification question regarding a program we are currently doing the screening. What is the timing or reporting of the process? Do they do the enzyme assay, -- typically done prior to reporting? I'm thinking in terms of impact on family, phenotype genotype correlation.

In Missouri, when they have a baby with a positive screen, then that baby is recalled for a blood sample that is sent to both confirm enzyme activity level, it takes like a day’s work and the blood is also sent out to a lab for genotyping, and the genotyping comes back within 2 to 3 days. I can't remember what they call it in Missouri, but there the genetic resource committee that works with the screening program, that works in tangent with the child's physician of record, to bring the baby in for that blood sample. That's about 1 to 3 mL they need to collect.

This is Dieter. FMA -- if I may comment on this as well, we provide some of the follow-up testing for the cases in Missouri. The cases also go to Duke as far as I know. What you have to remember, in the turnaround time for the testing is, laboratories that offer increment for a testing, for these conditions which we don't usually get a ton of samples, we run those typically once a week. However, for Missouri we make an exception. We basically request Missouri to let us know in advance when they will send a sample, so we can change the runtime to it day we expect the sample or so that they have the results quickly. Apparently, parents want to know if their child has one of the serious conditions. So that's an issue, confirmatory laboratories have to address one way or the other. The other option is, of course, you run a routine and the parents may have to wait a week to get the result.

Thank you very much. That's helpful to put that in perspective. I want to correct something I might have mistaken that was said before. If you look at Taiwan, the median age of diagnoses is around three weeks of age, unless I accidentally said three days earlier. I'm not sure if I misspoke, but if I did I wanted to correct that.

You also mentioned the two table approach in Taiwan? Appropriate DNA reporting then? Or is there another multilevel process going on?

It always makes me hesitate to talk about how the laboratory test works. It is not a genetic test. They take a second punch from the dried blood spot that they have and they run another test—specific laboratory knowledge. It is a two-tiered test but they do with the dried blood spot. If you look at the report when they describe using the two-tiered test, what they described in the report is they run the first test, and then request the second blood spot from babies that were abnormal on the first blood spot. Talking to the team in Taiwan, in fact they do everything off of the same dried blood spot now. The baby is not recalled for a second dried blood spot. It's just informing whether the screen test was positive or negative, and the essay as described, it happens --.

Thank you.

All right, if there's no additional comments I think we need to.

This is Dieter. One more question. I was wondering if anyone, about the cost again. Brad mentioned online and I can see there's only four states in the country that do not have a screening fee. So, they would only need money to basically start the program but then they would have the money from the fees to work. The other question I have is about the treatment cost. There are some states, and I believe North Carolina is one, where the treatment is paid for the condition identified through one screening by the state. I was wondering if any of the states interviewed here, is one of the goals as well, and how they feel about funding the enzyme replacement therapy?

I can talk about that from Missouri because we actually have that very issue. Because enzyme replacement therapy is expensive, those children who require it are going to end up, regardless,

getting it or likely getting some enzyme replacement therapy. So there was some anxiety about the cost to the Medicaid program of providing enzyme replacement therapy. The interesting thing though is, if are talking about the infantile onset disease, assuming the babies are detected, they're going to require enzyme replacement therapy either way. It's just the issue of whether they get it earlier and whether or not they are likely to survive longer on ERT and whether they're going to retire those that require mechanical generation. There are charges to do it cost impact analysis. It's complicated because like I said, it's the issue of the timing of initiation of enzyme replacement therapy. And I also see questions in here about the cost of implementing the test. [Indiscernable] can probably comment on this better than I can, but from talking to people the actual cost to do the test, not the cost of any of the following treatment which would undoubtedly be expensive, we are told is on the order of about $1-$2. It's more complex because you have to get the laboratory equipment, and the space and equipment and follow-up. Depending on the method, it's probably on the order of the test being $1-$2. That doesn't describe the cost. That's why in our report we didn't focus on issues of cost.

Alex, when you're talking about that—this is Chris—you're talking about the cost of the screening test, correct?

Yes.

And that's a small part of the whole process.

[Indiscernible-multiple speakers]

Dieter. And then somebody else?

Okay, about the cost, I was curious to know whether there were opinions from the state, otherwise I think in the United States of America and the cost shouldn't be a major concern, you have to eventually decide how to pay for it. I think there is money to do it.

Anyone else who wanted to ask a question?

This is Dr. -- I missed the discussion. You have a feeling on the ability to help the department implement the screening compared to SCID and Critical Congenital Heart Disease?

Hello. Hello?

Please remind folks to put their phones on mute.

Julie, do you want to talk about that?

In reference to the question of the states' ability to do screening for Pompe, I think Missouri's experience is that it can be done. The other is the readiness and feasibility. It relates around

other problematic issues, the authority to screen, the cost of the testing, the funding for treatment, the availability of follow-up. As that relates to the onset, it is broader. It is not just about the follow-up in the laboratory, it is the broader of the screening in the system in general. Relation to testing I don't think, there are states that are currently going through a number of validation processes for the different methodologies that are out there. I think that, that should not be an issue moving forward. The -- locations for each of these conditions that's been added, whether it SCID or CCHD, it is still from the same public health pot, whether increase in fees or statutes that need to be changed. The need to be done prior to adding this to the disorders, those things they can take time.

I would add that although the [no audio]

[The AC meeting will resume at 1:10 p.m. EDT].

Afternoon Session

Welcome to the afternoon session, Friday afternoon session of the first meeting of Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. We had a quick lunch. We are active and ready for the next session. We need to take attendance again. So go alphabetically.

-- Colleen Boyle, Denise Doherty, Melissa Parisi, Charlie Homer. Okay. We definitely need him.

Kellie Kelm, Fred Lorey. Michael Lu. Stephen McDonough. Dieter Matern. Alexis Thompson is not able to be here this afternoon. Catherine Wicklund. Andrea Williams. Debi Sarkar is here in this room. Frederick Chen, the American Academy of Family Physicians. American Academy of Pediatrics, Beth Tarini? American College of Medical Genetics, Michael Watson? American College of Obstetricians and Gynecologists, Nancy Rose? Association of Maternal and Child Health Program, Lacey Fehrenbach? Association of Public Health Laboratories, Susan Tanksley? Association of State and Territorial Health Officials, Christopher Kus? Department of Defense, Adam Kanis? Genetic Alliance, Natasha Bonhomme? March of Dimes, Ed McCabe? National Society of Genetic Counselors, Cate Walsh Vockley? Society for Inherited Metabolic Disorders, Georgianne Arnold? Okay. Charlie Homer? Fred Lorey?

Here.

Andrea Williams? Okay. Our presenters still need to get on. We will make sure we have contact with them.

Dr. Bocchini, Susan Tanksley is on.

Thank you.

If anyone else has gotten on, following the roll call, please identify yourselves. In the meantime we are looking for Charlie Homer and Andrea Williams. Apparently they have had a little trouble calling in but they're in the process of doing so.

I'm checking to see if Andreas or Charles has gotten on?

They are not connected as of yet Sir.

Please let us know.

I definitely will, thank you.

Charlie Homer is on.

Thank you Charlie, we are still waiting for Andrea. Are you aware of her being tied up with anything?

I am not.

She should be on shortly. I think, if you are the first speaker, we should go ahead and get started.

That would be great. I did send some slides this morning. If you could get those up, that would be helpful.

For this session, just a reminder for everyone, the committee members have been assigned to follow the evidence review committee and evaluate the data initially. This is to help focus the questions for the committee, and then make some initial determination from which the committee can go forward for discussion. Charlie, I will turn it over to you.

That is terrific, and again thank you. On my screen I don't see any the slides.

They are up.

So it's just my screen?

You are connected?

Yes.

Can everybody else see the slides?

We will make sure before we go ahead. We have it up on our screen so it's in the system. We need to figure out why it is not the case.

Now we are getting a different view.

Interesting. Still not there?

No.

Maybe advance the slides.

Charlie, nobody else apparently is seeing them.

Do you have the third slide Charlie?

It is on the screen.

Okay.

How about everybody else?

No.

Okay.

This is Andrea, I see the first screen.

Maybe people need to reload.

I see where some people need to reconnect and log back in.

So let's give everybody a chance to logout and log back in.

I heard Andrea, you are here?

Yes I am.

Any other organizational representatives that have joined following the roll call?

Okay. This is Lacey Fehrenbach.

Thank you.

Let me know when you would like me to proceed.

I would like to see if people can tell us, if other committee members and organizational representatives, if they have access to the first slide.

I do.

I do.

Okay, perfect. Charlie, you're set to go.

Terrific. Again thank you very much. Andrea and I have the pleasure to be the lead on this workgroup. Again, this is Charlie Homer. As everyone said this morning, I want to complement Alex and the team for doing a superb job, incredibly hard work, incredibly diligent in incorporating evidence at the very last minute. They've also been extremely responsive to questions that we have had in trying to clarify our understanding of the evidence, as we have sought to formulate our interpretation of that evidence and make suggestions to the rest of the committee of what we believe the evidence suggests, and how it applies to formulate our recommendation. If I could have the next slide. We jumped. This slide is a reflection of my work's efforts to produce a matrix in which we have reviewed as a committee. The critical point here is for us to make a recommendation, to move forward with incorporating a new test. It needs to have superior benefit and a high level of benefit, then we can have other considerations that we discussed about—feasibility, testing, implementation and readiness. We will use that framework as we have talked to the evidence that was presented. I do recognize, from the conversation this morning, that there may be variations in the interpretation of the evidence. That will be part of our conversation this afternoon. Next slide please.

So the next slide, we really divided our consideration into two parts. We recognize that this is a single test, and we have to make an all points decision based on the performance of the single screening test. Nonetheless, we think the considerations can and best should be thought of separately. We are thinking of the infantile form of this disease. Without the evidence was clear that the screening results and earlier diagnosis for clinical identification, we thought the strength of the evidence was that earlier treatment for placement therapy results for better output. There was discussion of that this morning. I think, still, I have a high level of confidence that infants, based on the evidence identified to screening and treating with enzyme replacement therapy, have better outcomes than historical controls. Those were identified through clinical, historical controls—meaning, in this case, through clinical recognition. Next slide.

The next question then is, are infants identified to screening picked up earlier and treated with ERT have a better outcome. The next question is, are the tests good enough, can you identify cases with a high level of sensitivity and specificity? Again, our interpretation of the evidence presented this morning is that the test is extremely sensitive for the infantile form. And, with

particularly the two-stage algorithm undertaken in Taiwan, there's also a very high level of specificity that there are relatively few false positives, which is of course critically important in a low preference disease such as Pompe disease. I'm going to this quickly, because it's meant to be a summary or an interpretation of the evidence, and the most important part is your conversation about this.

Next slide. So, if you look at the decision matrix—keeping in mind the decision matrix we have endorsed—the question is, is there a significant benefit? If you look at Dr.[Inaudible] decision analysis, once again I'm not presenting the confidence intervals but the point estimates. It felt to us that there is a significant benefit to screening, and 13 lives saved in the first 4 million, 26 infants surviving often later, based on screening -- off ventilator, based on screening. Looking at the certainty, the definition of certainty is what the likelihood that additional science will change that result. In our view, the likelihood that additional science would reverse those or change that, we thought was very small. So in that sense, it's high certainty of significance clinically. Again the test, we felt was highly sensitive and specific, which then raises the discussion of the feasibility of the test, which again was the subject of lots of excellent conversation this morning.

We will come back to the disability in just a minute -- feasibility in a minute. We wanted to continue the conversation about benefit. We felt the data that was presented, again there was discussion this morning, we felt the data was compelling, that there was significant benefit and high certainty for the infantile. And then the question, what do we do with the later onset? And how do we consider that group, given that there is a high level of certainty, a significant benefit, in the infantile group. We feel like in the outset, you can use the same criteria that you use for the infant group and say you need to have a significant benefit, with at least higher moderate certainty to make a recommendation. You can take any nonnegative -- again with a high level of certainty. Or collaborating on that even further, any nonnegative benefit then that is confident that there is not harm associated with identifying the late onset group, those been providing additional guidance as this committee has been in the past, for studies for the optimum management. Of advent of -- individuals identified to screening of late onset. That was the genomic testing, we can discriminate quite readily between the infantile onset and the later onset. Our believe of the liaison group, in conversations with a third of these, was actually the right threshold for criteria to use, which was what we wanted to be confident there would not be harmed, and we felt that if there's confidence there isn't harm, this is an optimal situation for making recommendation for a study to assess the management.

Next slide. And again to reiterate what was said this morning, it is clear that there are no direct data available on the impact of treatment prior to the onset of symptoms. For late onset disease, it is clear that treatment after diagnosis results in improved function. Boost on function and system. As Alex highlighted this morning—quite different than clinical evidence. Again, the evidence presented good information about likelihood of harm associated with treatment. Again, the studies of treatment, in the late onset study. For example, it looks like there was a pretty similar profile of receiving ERT versus placebo, and a higher level of allergic reaction but it development in general that was relatively easily managed.

Next slide. So again, just to elaborate on this a little more. It's a credible hypothesis that treatment prior to symptoms, or clinical diagnosis, benefit. But no data, and the harms are not zero. I do think we should acknowledge, in this case, the lived experience of individual in the reports of difficulty, in the time to come up with ultimate diagnoses, and certainly among those who are diagnosed later, their articulated preference for earlier knowledge of their diagnosis. And that's more passionately and more articulately this morning than I was able to make.

Again, from our perspective, this provides an optimal context for trial of alternative strategies about early treatment. So complicated, early treatment of late onset treatment.

Next slide. Now there was a lot of conversation this morning, and the excellent studies that were done in the survey of states. It is clear that states would not be able to implement testing tomorrow. That seemed very clear. There does seem to be some uncertainty about which of the tests out there that are optimal. And also seems clear that all of the tests are acceptable. In that regard, the approach that is used, there would be resources allocated to training, staffing, purchasing or modifying equipment, and establishing relationships with specialists to provide care. So again, we felt these were not hurdles that were vastly different than other screenings' recommendations. So we felt this to be in the intermediate category that is not ready for immediate implementation, not truly insurmountable barriers. The barriers that did require recognizing will take time for implementation, and we should make a recommendation.

To the next slide. Taking this all together, our recommendation with that, liaisons to the workgroup, based on our understanding of the evidence is that we would recommend adding Pompe disease to the RUSP, and this would fall into the A 2 category of readiness. Recognizing the difference --. And so that would include something like a 1 to 5 year rollout for the states to obtain equipment, train staff and develop referrals. This recommendation should be coupled with guidance, to provide support for a trial or study of alternate strategies, for the treatment of the onset of the disease. And I think that is our last slide. Andrea, I don't know if you want to add anything to my summary.

Please have Andrea Williams line open.

Thank you. I don't have anything else to add to what you already said. You did a great job, as to what we discussed.

Thank you Andrea. Thank you to you and Charlie for the work you have done to organize this presentation, and the rationale that you use to come up with this recommendation for the committee, to now discuss. Could we put up the matrix? Dr. Homers second slide.

This opens the line of the committee, those members at this time. The organizational representatives I would like to hear comments, questions, discussion, from the committee to determine whether there is -- let's just go ahead and begin the discussion.

It's a very quiet committee.

This is Coleen. Let me ask clarifying questions in terms of action, moving forward. Is there a difference between A 2 and A 3 in terms of RUSP approval ? I guess I'm trying to remember back? Does anybody remember that?

I think we did this sort of timeline, where we felt that it didn't change the recommendation by adding to the RUSP. It indicated potential timeline. For example, at this is another test to be added that could be done in a lab with no additional personnel, everybody ready, that would be a A 1. A developmental stage that would take one to five years for the states to be able to add, this in terms of personnel etc. And unprepared would be a situation where it is unlikely that any state could put together what is needed to have something done in less than five years, the general mark that we used. It would not necessarily indicate a difference in the decision that the committee made, in terms of evidence of high benefit or high certainty benefit.

So let me ask Andrea and Charlie a clarification, in terms of A 2, and the recommendation of further evidence for treatment for later onset, does that factor into the timeframe or would we have to, is your recommendation that that has to be in place, how did you think of this moving forward?

So I guess I personally didn't think of the A 2 versus the A 3. I think I'm more comfortable saying A 2. I was more thinking of that is simply the ability to effectively implement the testing process and procedure and make sure people were linked into the newborn screening programs worked on that, in the capacity for services.

So the fact that the majority of cases that are being detected would be late onset, you are comfortable with moving forward, or your recommendation is moving forward as is, based on what we heard as the standard treatment protocols available, within that context, with the condition that there also be some new additional information as this rolls out to capture those people in clinical trial or capture observational data. I'm just trying to put your recommendation in some context.

You are stating that exactly right. Based on, we needn't wait for additional studies to rule this out. It is really a question of the feasibility for the laboratory, the public health laboratories to gear up to undertake the test and establish mechanisms to connect those people identified with services.

This may be a nuance, but I will throw it out there. There is the recommended panel and the secondary panel. Have you thought about having the infantile on a recommended panel and later onset on the secondary panel? Perhaps how that might play out, I might ask Mike to also talk to that as well. And those of you in practice as to how the secondary panel works.

We were told they could not be differentiated. I might be wrong.

This is Alex. At the time of screening, you cannot screen just for the infantile.

I realize that, but that would be like others, the target would be infantile, and they would be secondary conditions that are identified which do or don't have evidence yet to suggest benefit. That puts that in a different category, saying let's collect information to clarify the health benefit there. They can all be screened, but the target I guess would be the infantile onset Pompe disease .

Just a thought on how to move forward.

This is -- can I ask a clarifying question. If something's on the secondary panel, is it required to be reported?

Can anybody answer that question specifically?

From the public health letter?

This is Grant, I would say since it's not required to be screened it would be required to be reported.

-- Would not be required to be recorded.

From my perspective then, the problem would be that you would have the benefit of potentially following these individuals and be able to determine when they need treatment.

Can you hear me?

This is Dieter. I must have been muted. The question about the primary and secondary targets, I think you could do it here but only if you included testing in the screening process.

That will add a whole layer of issues, I think in the cost and so on. Otherwise, I agree with the A category. I still don't like the other rating group in the matrix. I think we should either recommended are we should not recommended. If we see that the states have time to look at it and get the stuff in order, my concern remains that if they don't have a clear recommendation, that they should be included in the program. It would cause significant delays, you would have the situation, which is starting already, where some states will screen part and others will not, and basically we get to the beginning of the advisory where the issue was.

Can you hear me? I was muted. I think it's more complicated than that, because do we want to identify—other to have the same newborn screening results. I doubt that the newborn screening program is going to be the one that's going to discriminate whether it's early onset or late onset. If that happens in the diagnostic end of those people are tagged and labeled and in the center of the system, and anger asking the diagnostic people, but you can ask them to not

deal with this situation. So, late onset people will be labeled as possibly late onset and when they turn 21, until they have interesting problems to deal with, with insurance and whatever. The other issue on the secondary target, even though when we did the original divining that, they said they were secondary to the primary targets of screening and were not, there was no guarantee that any screening text was going to identify them. In fact I think most states have actually mandated that they are screened for it, and whether they will distinguish between these two categories for Pompe disease differently than they did for all the other conditions , I don't know.

Mike, those are routinely reported out?

As I understand it, the secondary, what we call secondary targets became mandated targets in many states. Even though we didn't argue that we were maximizing screening for them and didn't think we do enough about them to put them on a primary list.

I do think that once they are in the diagnostic world, to have a diagnosis of earlier or late onset established, they are in the health care system and will be followed. We will be accumulating information at a local provider level. That will be very important to figure out how we capture it centrally as we go.

That's a pretty long window, between finding it at birth in dealing with the preclinical markers. Wouldn't Juergen introduce these therapies? It seems pretty obvious from the evidence that once the muscle wasting starts, you have to get in early, and the question is when do you start the therapy.

I think capturing these cases, these people, it's just critical in terms of rolling this out.

It might be a retrospective study that could be done with dried blood spots, but that takes time. Clinical information to the state program, which is verboten, unless we got some form of consent. I guess is we are not well aligned between the onset of the disease and the likelihood that the spot is still there.

This is Cathy. Can you hear me?

You and your dog.

The one time I'm not muted. I had a question, if we recommend the one to five-year rollout period, there are states that have, in the state legislation, that is something is added to the RUSP they have to add it . How does that change how soon they have to roll it out?

Based on what we say?

I don't think any recommendation that we make, approved by the secretary, has a timeline to require states to make a decision about it. Essentially, all we are doing is we made it A 2, is

recognizing there will be a period of time before every state is likely to be able to include this in the RUSP. It wouldn't change the fact that the recommendation is to include it in the RUSP , and that some states may be the leaders and ready to do it or could do it in a shorter time period. It doesn't define the time period, just the expectation based on the evaluation and the public impact portion. Obviously this is the first time we are doing something -- I think the important thing is we are not trying to define the time period, but the expectation is that things need to be done, and recognize that those need to be done along with a recommendation to be included.

This is Don. Maybe I'm wrong about this, but I thought this major close -- matrix was for our benefit to explore or talk about our recommendation is simply whether it's included in the RUSP or not . If we don't want to include in the recommendation the levels, is that right quick?

I think we were asked by the Secretary to include a public health impact. And so, I think is critical that we do include that assessment.

This is Susan Tanksley. I think my line was muted. I wanted to comment on that, and I appreciate the recognition of the time frame that it would take to implement. Speaking as a newborn screening program representative, it takes a significant amount of effort and time to get through all of the processes. This is emphasized in the diagram that Jelili presented this morning; that it is a process, not that newborn screening programs don't want to add a condition, or even the newborn screening program has a choice in the situation where often it is the decision of power that is much higher than the newborn screening program whether a condition is added in a state, and that might be an entirely different issue to talk about. I know that was mentioned in one of the subcommittee meetings yesterday. The disparities between states are arising again, that's a different issue I want to voice—that as a newborn training program representative, it will take time that the program can certainly do it. It's not that the test cannot be done in a lab. And in regard to whether the late onset is a secondary target or initial target, my understanding of the secondary target, and especially in the case of this, is that typically the secondary target is identified through differential diagnosis while you're screening for the initial, for the core condition, which in this case is the early-onset cases.

Thank you for that comment, Susan.

This is Fred. I would like to back up what Susan said. Newborn screening is a system for us doing the actual screening, not just a lab test. This statement in one of the slides that we saw, no major barriers to -- could not be further from the truth for us. It never is for any disease. It is even much more so with this, for some of the things we saw this morning. No disrespect to the folks who prepared this, but to me that is very rosy assessment of the evidence that we saw this morning. Again, there is a statement in there about lives saved. You can't talk about lives saved without a time factor. Are lives saved permanently, or averted for a year? That was based, my understanding, on the Taiwan study and partly on modeling because you had a denominator of 4 million. Those are not real data. We are still dealing with, in the United States anyway, one case of early-onset from one state and zero cases in the other, with the majority

of cases being the late onset which we don't have good data on. I also object to the statement, in one of the recent slides, that we can make a hypothesis that early intervention helps early-onset that there's no data. We are scientists; we go on data.

That's a hypothesis.

Why have that in there, when we are dealing with the disorder which we are seeing today, the vast majority of cases we pick up are the late onset. -- The issue also increases mild to -- [indiscernible-multiple speakers].

It's 40 to 60. Can I finish without interruption? There is significantly more cases, than what we saw this morning, that are late onset. In the United States we have one in one state, and zero in the other, of early-onset. The screening folks have not tracked or followed late onset before. That also makes this more difficult. I don't know, I'm always feeling like I have to stand up for the newborn screening folks because some of these things are glossed over.

This is Andrea—with all due respect I think that the linking of life has an impact, when you think about screening for disorder, and I'm only getting get 30 years. I am very upset about that because if it is your child, you wanted as long as you can get it. I want my child screened at birth; I really think it's important not to make that particular case. That really brings out some emotion.

Thank you.

It's a Catch-22 when it comes to late onset because if you say you need the study before you can screen for it, you don't identify the test as presymptomatic and you never get the evidence. I think we want to identify the early-onset cases and treat them. I think there are guidelines out there that would help geneticists and neurologists to see these patients to determine when to start treatment. Yes, not all of the work is done but I think that should not keep us from moving forward and get this rolling.

This is Kellie from the FDA. I have a question. The screening methodologies, are we ready to go or is the message is that it’s available for immediate use for states. We don't have that -- do you want to comment on that?

I am not using it, but to answer your question it is only Missouri. Doses in the validation phase with the compilation screening right now. The other methods, which have been discussed, have not been validated for newborn screening purposes. Population newborn screening purposes, and that is something we would have to take into consideration.

This is Dieter. I think it comes to the method, as available as any other, for a laboratory developed test. I don't see any issue there. The drastic and logic methods, in the past, have had issues where availability of either hardware pieces or reagents was not consistent, as far as I understand they are working on this and it's been pretty smooth over the last several months,

whether they would be able to roll it out for 4 million babies I don't know. I think that the fact it's not happening overnight anyway, it will be ready. When it comes to the third technology not mentioned today, immuno capture method, there is currently nobody available to provide a timeframe necessary for that test, for Pompe disease at least . I don't think that is can be a big player in the future, and let someone was interested enough to work on providing these reagents on a larger scale.

This is Jim again. I agree with everything -- I would also like to point out that, in fact, is one of the ways we are looking to use for population screening, for newborn screening, for Pompe disease. As I understand it, they would need to do dedicated machines. If that is the case, that is a significant cost or additional cost, not only to the state program in general but to the newborn screening system, where these are the kinds of things that we pieced out in the readiness feasibility screening for Pompeii, at least on the state newborn screening program. Just using mastectomies, for an example. I'm not sure about the AOL as it relates to how effective it will be right now or in the immediate future for population screening.

This is Dieter again, if I may comment on that as well. Any condition that has been brought forward to the advisory committee in the recent years, MPS one disorder, Pompe disease, all of these would require additional equipment in the laboratory. For some laboratories, -- Pompe disease, they potentially would have capacity on their existing equipment to do with a limited population, but otherwise I agree the new equipment is required, independent of whatever condition comes online. That is true for SCID as well.

Are there other questions?

This is Coleen. I think this has been a great discussion. I think there has been great evidence-based review. We have had lots of public questioning comment. I heard a few things I guess I wanted to circle back to. One I heard earlier on, by Fred, the suggestions that we do, that there be more formal pilot programs, state pilot programs perhaps similar to what was done with SCID. We really get a good sense of what's going on in terms of clinical phenotypes, genotype relationships and how that relates to the implementation of newborn screening. And also, I'm still debating in my own mind, the target, the RUSP panel in terms of target condition and the secondary in terms of infantile and late onset. Whether given that this is a very new, somebody said earlier paradigm shift, a better way of going forward with this? In a carefully, and we can craft a recommendation around that, but I want to put those two ideas or opportunities out there, in terms of having further discussion or at least considering them in terms of the recommendation.

This is Melissa, if I could make a comment about that. It seems to me that from the evidence that we reviewed, that any of these conditions could end up being on the RUSP, represents a severity at onset. I think separating infantile classic forms, although clearly that the targeted population where the benefit is most obvious, and the later onset forms it would appear there's likely to be benefit from early treatment, we’re not sure, it's a bit of an artificial separation

when you're really looking at the spectrum of the disease. I would encourage the panel to not try to divide Pompe disease into primary versus secondary targets on that basis.

This is Dieter. I would agree with that. If we consider pretty much any screening condition to do the spectrum of disorders, typically the milder ones are more frequent than the more severe ones. To discriminate between, if we try to do the early and late onset, we would need molecular and we don't have that. The next question is, how would you deal with the result with no activity, and a genotype that suggest late onset, would you just call them again in a few years or would you ignore the result and forget about it? Logistical and ethical problems goes beyond, in my opinion.

This is Fred with the AAFP. To go on record, if we are combining early and late, calling in the question for the level of certainty of evidence, that question raised this morning as well. As we look at the matrix with certainty, especially as you combine them in the more moderate category for me. Also, calling the question of overall benefit and how significant it is.

Thank you, Fred.

This is Charlie. Just to build on that, that was why, even though again it is a spectrum, there does seem to be some distinction in how these conditions appear. And certainly I felt interpreting the evidence was strong about the infantile form. It was certainly not, with any level of certainty, there is benefit for early identification for the late onset. That's why I thought the threshold should be different, that was what we recommended that for the late onset. We want to be comfortable there's not harm. And that was why we put it in.

I am still confused, to be honest, about primary versus secondary RUSP categories and the implications of separating them. It does seem to be once the children are identified, regardless of genotype, they need to be hooked up to new appropriate services and active within appropriate provider. Ideally for the later onset types, they would be entered into the tracking study or more active study.

Any additional questions or comments? We think that, based on the discussion, it would be difficult to have primary and secondary targets, an attempt to deal with them at a state level and how to follow up, it would seem Pompe disease was the single target , then it would enable evidence to revolve concerning the outcome of early identification, or treatment of asymptomatic individuals in a scientific perspective way. Which I think would benefit by having Pompe disease as a single target. It seems to be the consensus, at least from the people who spoke. So are there any additional questions or comments?

This is Andrea. I am still, I still think because the infantile, we can worry so much about the late onset at this point. We need to add this to the RUSP and move forward. Whatever type of research comes after, it can be dealt with at another time. I think this is a time where we need to really think about what the evidence has shown, the benefits of screening for infantile, and

move forward. We have waited so long to get here just to start taking it apart again. I think that we can move forward.

I think I would entertain a motion for whether to recommend the addition of Pompe disease to the RUSP, with the recommendation as originally indicated as an A 2, or at a different recommendation.

This is Dr. McDonough. I recommend that Pompe disease be added to the RUSP, and that we have some supporting documentation, right matrix with criteria to be added to the RUSP Thank you Stephen. And you would make that an A 2 as recommended by the members who did the initial review and the presentation?

I support that. The framework I know -- says added to the RUSP, if we're going to do it and not say it's in A 1 -- A 2, use the matrix to determine if it meets the criteria for the RUSP. I don't think we need to distinguish those we have taken that under consideration.

I think we can do that by making it a recommendation, indicating the issues that we feel need to be addressed, or tied to the public health system, to enable this to be included.

This is Charlie. I do think, whether we call it A 2 or not, I think the emphasis on the implementation of this not being treated, we need to bring that out. Hopefully that will be associated with resources.

I agree that has to be done.

This is Dr. McDonough, I think anything we add to the RUSP, we should expect that the states are granted take 2 to 3 or 4 years, the majority of them to get it done.

It's going to take a while, and listed sent A 1, anything other than that will take time.

I believe we need to clarify those, going forward, with any condition that we recommend for RUSP. Do it based on the requirement to address the public health and limitation. We need to list those things. Our matrix does amount as a A 1, 2 or 3. That will really help us.

This is Dr. McDonough, include A 2 in the recommendation.

Is there a second?

This is Don Bailey, I second.

With the motion to approve at an A 2, with the second, are there any additional questions or comments?

This is Coleen, is there a way to make a recommendation that there is a formal multistate pilot program? To help guide implementation.

This is Dieter, doing that right now basically. Missouri, and New Jersey and Illinois will follow. I don't know if we have to make the recommendation because they're doing it anyhow.

[indiscernible-multiple speakers]

This would be a way to standardize it and to collect systematic data over time.

And hold off making the recommendation?

No, not hold up with it.

So you're asking, Coleen, that the recommendation be made to include that data from the initial states that are implementing this service, pilot studies, to help clarify the best test or best protocol.

Correct.

I think that is a reasonable thing to make, that is, a motion?

Yes.

If you do, then Dr. McDonough, will you accept that is in addition to your recommendation?

Sure, if the committee members support that.

Can we reframe this? I'm not sure I understand what we are voting on.

That the states are either implementing, or currently implementing according to Dieter, that several others rolling this out based on state legislation. Coordinate activities to develop systematic information within the -- we can't talk about funding, so we have to talk about the fact we need to coordinate state activities to use that as a framework for developing additional, this is long-winded, that's the idea.

This is Dieter. Maybe Mike wants to talk to this. As part of our study that we are conducting, we had funding through -- to set up the same process and chronology for the limitation in region four. There are online tools, if you want to suggest the states actually enter data and help others to move this forward, then I think it would be fine. I think -- might have other opportunities to help states to move this along. I think any addition that we make to our recommendation might have unintended consequences when it comes to the actual implementation of the screening.

I agree with what Dieter has said. Maybe the recommendation is too many qualifiers complicating the interpretation of the recommendation. I think it's going to happen anyway in terms of the coordination of the pilot studies, whether we put that formally in the report or not.

-- I think we are being told that the recommendation really needs to be whether to include Pompe disease in the RUSP , and any other things we recommend would be in the Secretary's letter but we don't have, we can't add multiple clauses to the recommendation. As it stands, we need to make our have a vote on Dr. Madonna's original recommendation, and then we can talk about other things. That last comment is very true, as a natural result of this data that is developed from the states will be used by other states as sort of a pioneer stage, which will result in other states learning from their experience and modifying what they do based on the effectiveness of the program. It certainly can be dealt with, the way we are doing with other things that have been recommended by the committee, in terms of following and making states aware of what the outcomes are in recent publications, about the critical congenital heart disease implementation. I think that, we need to go back to Dr. McDonough's original recommendation. And go from there.

This is Charlie. One further question related to that which was, I like the idea of clarity of the recommendation but we also suggested that there be careful tracking and/or study of late onset as part of this. Is that part of the recommendation or part of the letter?

That will be part of the letter. The other things that the committee recommends should happen with the inclusion of this in the RUSP. That will be part of the letter to the secretary

---

This is Chris. I guess the comment, and I agree with the idea of having a clear recommendation, but when you put in things like coordination tracking, is the responsible party, what is the funding, those come into play.

That is a good point. Again, our program for long-term follow-up, I think it's perfectly nice in here for a framework that's already set to do this.

We have a motion and its seconded, it that we need to go forward with the vote. I'm going to start alphabetically -- first of all we need to see if anybody will abstain from the vote.

This is Dieter again. We have the ongoing study and part of it is Pompe disease, does that mean I should abstain from voting?

I don't believe so.

Okay, thanks, I don't think that represents a conflict

Extension -- abstentions, Don Bailey. I will vote yes.

Coleen?

Yes.

Denise?

Yes.

Charlie Homer

Yes.

Kellie Kelm.

No.

Fred Lorey.

No.

Christopher DeGraw will vote representing HRSA?

Yes.

Dieter.

Yes.

Melissa Parisi.

Yes.

Catherine Wicklund.

Yes.

Andrea Williams.

Yes.

And Dr. McDonough.

Yes.

I'm sorry I have you, I'm happy that you were able to get online for this, the latter part of the meeting.

I got a standby ticket, so I got lucky.

Okay. So that recommendation passes. We will bring that forward to the Secretary. I think it is a general consensus that we also adopt the guidance that has been given by the committee members, to include in the letter to the secretary, related to evidence review and public health impact. We include a summary of that data and the additional recommendations relative to the late onset disease, in terms of the difference and level of certainty, for identifying those individuals from that perspective study that might be performed [indiscernible-static] and included. Any discussion on those issues?

Sounds good.

All right. If there are none, I think, I really appreciate the amount of work that has been done by a large number of folks. And first of all, the Discretionary Advisory Committee Charter, in terms of going ahead with the original plan of the Secretary's Advisory Committee, was to review the data at the May meeting. I want to thank the evidence group for a wonderful job in providing us with clear and very thorough summary of the available data, and the first time we included public health impact as well as decision analysis and data. Those were very helpful in forming a decision. And the work with the committee members who serve as liaisons and working with the committee in reaching this vote on Pompe disease. I want to thank HRSA, and dealing with the issues that are related to a webinar, to tie in for the decisions. I thank everybody for their work.

If there's any additional comments? Then we will adjourn the meeting. Thank you all for your efforts.

Thank you.

Thank you.

[Event concluded]

Addendum to Transcript – May 17 Webinar

Chatbox discussion during Friday morning session

Dean Suhr - MLD Foundation:
Will copies of the presentations be made available for download?

Lisa Vasquez:
Yes. within a week or so via the AC website:
http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/meetings/index.html

Jeremy Penn:
Lack of statistical significance is not a big surprise because of the small sample sizes.

Chris Kus:
Could we put up the slides that are being discussed?

Priya Kishnani:
What worries me, is that some of the comments, like not real change between less and older than age 3 months- the difference is life vs death, or being on invasive ventilation vs not. The treatment does work. There are children of age 14 years and participating as functional members of society.

I hope decisions are not being made based on whether state has the funds to do it today, rather is this a condition worth nominating for NBS.

I think seeing pictures and videos will bring to better light, the difference between those picked up clinically vs NBS or in the first weeks of life

Stanton Berberich:
"Worth nominating" indicates an assessment of value. The benefit must always be assessed in context of cost. Therefore, decisions must take into account the funds available to recommend addition to a state's mandated panel.

Priya Kishnani:
I am a bit cynical, at this time, no state has any additional funds so no condition could go through, as there is lack of funding to implement and Follow Up. I remain hopeful that the data is the driving force- outcome is significantly better (life vs death) when identified by NBS.

Brad Therrell:
Since all but 4 state programs have a screening fee, the funds issue is really related to start up funds. Beyond that, the question revolves around issues necessary to adjust the screening fee.

Jeremy Penn:
What is the cost of a screen for Pompe?

rsingh@emory.edu:
Any studies done in the impact on families for patients diagnosed by clinical symptoms vs. NBS, that can be huge.

Priya Kishnani:
Cost is, I believe, $1 per patient. The question of whether states are ready is one that would be true for any condition that is being considered, not Pompe alone. I am unaware if this was done for SCID?

Brad Therrell:
I believe that this is the first condition for which a formal assessment of public health impact has been included. This was a concern, previously, that has now be formalized in the process.

Debi Sarkar:
Dr. Therrell is correct. This is the first time the evidence review includes a public health impact analysis.

Priya Kishnani:
It just seems a new bar every time Pompe is up for review. Just some frustration for me as someone who cares for these patients.

Charlie Homer:
We have not been specifically asked to address cost-effectiveness per se in our deliberations

Dean Suhr - MLD Foundation:
Is there a current written summary of the decision criteria for a RUSP recommendation? The SACHDNC web site has the original ACMG report and the application form - but I could not find the criteria in a summary form.

Sylvia Au:
Public health impact is more than just in the NBS lab or follow-up program. We do have families living away from urban centers and lack of specialists to care for families, whether or not they live in urban centers.

Debra Freedenberg 2:
In Texas we fund a very small proportion of children who have been identified with a condition by NBS (payor of last resort). Since there is very limited funding for this program, we do not cover the extraordinarily expensive therapy but help facilitate funding sources that are not public health funding.

Debi Sarkar:
To Dean Suhr - please see Dr. Kemper's presentation during the Sept 2012 meeting "Final Condition Review Matrix"

Dean Suhr - MLD Foundation:
Thanks Debi!

Dean Suhr - MLD Foundation:
Debi - I remember that presentation. What would be very helpful is to summarize this in a 1-2 page text document and to be clear that this is the formal policy and process. There are many presentations - it is difficult to determine which are policy and which are discussion.

Debi Sarkar:
Thanks for the recommendation.

Debi Sarkar:
We'll work on that asap.

Chatbox discussion during Friday afternoon session

Katharine Harris:
NBS Programs test for analytes and generally not directly for a disease. The analytes suggest a panel of conditions that the clinician works to clarify which one to use as the final diagnosis.

Brad Therrell:
Some state laws require adding conditions if they are included in the RUSP. It is not clear how a recommendation of 'within 1-5 yrs' would play out.

Sylvia Au:
Once the disorder is on the RUSP, a state is at risk for being sued for not screening, even if you think it might take up to 5 years to be ready to screen.

Cathy Wicklund:
Thanks Brad, that is exactly what I was trying to determine; how does this affect those states that have laws requiring the addition of the condition.

Robert Ostrander:
Certainly CCHD is taking a time to roll out; it seems to me that adding something to RUSP is the beginning of that--and the time will depend on the condition. Especially as we move to more POC tests, this will be so. Unprepared should exclude, but developmental will be the norm.

Brad Therrell:
Cathy, it would likely depend on how much advocacy came into play. The Legislature would make the final interpretation or the Attorney General.

Srinivas Naga Chadaram:
Without screening, how will you ever know that they are early or late onset.

Sharmini Rogers:
Missouri actually has detected two early infantile onset Pompe, one classical and the other non classical. Both infants are on treatment.

Anne Comeau:
Clearly people want to study, and there needs to be a mechanism to enroll - whether madated NBS is the appropriate mechanism....we also don't know how the kids will do at 4, 5 yrs – hopefully well, but we don't know.

Kimberly Piper:
While these may be "recommendations" they have the effect of a mandate for states implementing the programs.

Sylvia Au:
Working in public health, we have to deal with children's health and life issues daily. Fred is just discussing Pompe in the context of public health impact in the whole. Kudos to him for bringing these issues forward. It would be different if public health had unlimited resources and we could do everything we want to do to keep children as healthy as possible.

Debra Freedenberg:
Dividing the same condition into primary and secondary, based on time of clinical expression, seems pretty arbitrary. Mike is right– clinicians will make the distinction, not the NBS program. The clinicans that generally treat Pompe are biochemical geneticists which every newborn screening program has a referral pattern in place. The issue is that there are limited numbers of biochemical geneticists.

Mei Baker:
Sounds like screening pilot studies are needed

Kimberly Piper:
A carefully evaluated pilot before a recommendation to add a condition to the RUSP is a great idea.

Anne Comeau:
Yes, screening pilots, just like the clinical monitoring for late onsets is needed.

Brad Therrell:
I think Coleen has a good point, given that this would be the first clearly late onset condition. Some programs have included conditions as a core target with high certainty and high benefit and left the others (like late onset) to the secondary group.

Rani Singh:
I agree, the disorders we are screening have a spectrum and we have some now we which have late onset forms. But monitoring the patients on a less frequent basis but tracking helps provide appropriate interventions in a timely manner. It will be helpful to be able to have a centralized data repository .

Anne Comeau:
Brad, I don't know what you mean. There'll be one screening result, and they'll all be reported.

Brad Therrell:
Anne - yes but the diagnostic data could be separated if the program had a problem with the concept of late onset newborn screening.

Anne Comeau:
well, I don't see that,...we just ignore?

Sylvia Au:
The NBS follow-up programs would still have to provide follow up to the late onset cases. We don't just send the result and do nothing.

Brad Therrell:
Right Sylvia. I am only looking at whether some will criticize the detection of late onset, and this is a way to get around it. The target would be early onset and anything else would be secondary.