DACHDNC Meeting transcript for May 30, 2014
Day Two
Transcript

All Right. Good morning, everybody. I like to welcome, everyone to the second day of the fourth meeting of the discretionary advisory committee on heritable disorders in newborns and children. I hope everybody had a relaxing evening so that we are ready to start this morning. We need to start with roll call. Again, we will go alphabetically. Jeff Botkin. Colleen Boyle. Kellie Klem is going to join us on the phone if possible. Is Kellie available?

Operator:
Dr. Klem, if you're here, please signal me by pressing *0.
Mr. Chairman I don't see a signal.

Joseph Bocchini:
Thank you. Joan Scott for Michael Lu. Steve McDonough. Deter Matern. Melissa Parisi. Cathy Wicklund. Andrea Williams. And our DFO, Debi Sarkar.

We do have a quorum. Now for organizational representatives, American Academy of Family Physicians, Freddie Chen. American Academy of Pediatrics, Beth Turini. American College of Medical Genetics, Michael Watson. American College of Obstetricians and Gynecologists, Nancy Rose. Association of Maternal and Child Health Programs, Debbie Badawi. Association of Public Health Laboratories, Susan Tanksley who should be on the phone?

Susan Tanksley:
I'm here.

Joseph Bocchini: Association of -- Chris is not here yet. Department of Defense, Adam Kanis by phone?

Unidentified Person:
Mr. Kanis, please signal me by pressing *0 if you are present. I show no signal.

Unidentified Person:
Mr. Chairman, I show no signal.

Joseph Bocchini:
Genetic Alliance, Natasha Bonhomme, who should also be on the phone?

Natasha Bonhomme:
I'm here.

Joseph Bocchini:
March of Dimes Siobhan Dolan. National Society of Genetic Counselors. Kate Vockley (Here). I think that's all individuals I see at the moment. And thank you all. We are going to now move into our first discussion for this morning good Jeff Botkin, committee member from the University of Utah is going to discuss conducting research on

population-based screening. As you know you give us a preliminary view of this and we have some discussion about it at our last meeting and now we will have a more formal presentation. So Jeff?

Jeff Botkin:
Thank you. What I'm going to do today is largely reiterate what I did on the phone at our last meeting. Maybe slightly more detail. I really want to leave time for discussion about this going to try to fight through these comments really quickly. There's nothing here that I think is not quite familiar to everybody in this room. I broke it already. We are working on technical details for those of you wondering at home. We are having a technical problem. You want me to work without a net?

[Laughter]

Joseph Bocchini:
It is up to you.

Jeff Botkin:
I do have my own computer but thank you. Let me pull that up. There's not much to look at with this presentation really.

[Laughter]

Jeff Botkin:
You can kick back and imagine. Several key points to begin with. Obviously the Discretionary advisory committee, the Secretary advisories committee if we change our status it really embodies an evidence based system, but a robust evidence review system as we are intended to be really requires robust evidence to review. So screening programs outside research context for my standpoint really don't provide adequate information for bodies of this nature to make decisions about screening. We also understand the import of the decisions that are made here and we all have struggled for years with making very difficult decisions on oftentimes a shockingly poor database. I think with the evolution of the system that has been developed the next stage really has to be try to develop an infrastructure to help support the acquisition of data to make decisions on a more thoughtful and informed basis. Again as we all know we're talking about 4 million babies a year in the mandatory screening program both of which demands that we'd be making decisions with the highest quality data available. Evidence is necessary of course on a variety of aspects of conditions that come to our attention here. The natural history of the condition, the range of clinical manifestations, Associates between phenotypes and genotypes. The key of course is efficacy of early detection intervention strategies. The adverse effects of course of detection and treatment alternatives and the cost effectiveness as well. The system of course has become much more uniform from state to state over the past decade or so. Yet the claim here is that that the research infrastructure evaluate the efficacy and safety of new and existing screening modalities is entirely haphazard. A fairly strong word but I think it

is an accurate description. We really have no system to formally evaluate these critically important screening tests and systems. The test article is the system itself. Obviously it is not the test itself, it's not the intervention but it is the whole system that goes from the acquisition of the blood spot through to the long-term support for the child that we help leads to improve morbidity or mortality statistics so as we assess new conditions for inclusion on the RUSP, I think we have to evaluate the system itself and not subcomponents of that system in order to make the sorts of decisions. From my perspective I think this is too controversial but all conditions -for inclusion on the RUSP should be evaluated through population-based pilot studies prior to adoption on the RUSP. So what are the barriers to this type of research? There are a number of them that we have to work through over time. Obviously newborn screening is a state health department-based system. State programs don't have for the most part a research mission or budgets not it's simply not part of their typical portfolio and I guess certain states they are actually prohibited from doing research. In many individual state populations are also too small for research on rare conditions or at least the decision-making would take a long period of time because of lack of adequate kids within the a state system. The system really relies on research that is investigator initiated and dependent on collaborative state programs. Thank you.

I had the presentation once where the bullets were changed to dollar signs. [Laughter]. Somebody thought that was a commentary about something.

Correct slide, thank you. The System relies on research that is investigator initiated dependent on collaborative state programs but substantial variation in acceptable designs as far as state programs are concerned and this has been a particular issue at least from my perspective say with parental consent models and that has been a barrier in certain circumstances to conducting this type of work. These projects are large, expensive and they raise interesting ethical concerns. I also think there is frequently limited commercial incentives to attract commercial sponsors of research for this -- this really does need to be largely a publicly funded Enterprise.

I don't know whether I'm the one – moving back to my machine --CF remains really the only condition on the RUSP that was evaluated prior to national implementation through a randomized, controlled trial. Policy is often made from studies with small number of cases and outcomes assessed through comparisons with historical controls. Next slide, please.

Here's a schematic that I proposed a few years ago and will refer back to just very briefly today. Phase 1 sorts of research can be done prior to the population level. You can get some information from outcome comparisons of siblings, for example, about whether early intervention to likely to be helpful or not. But the Phase 2 is assessing the benefits of population screening and we're looking at the system evaluation. Phase 3 and 4 an economic analysis and post implementation of evaluation. Next slide, please.

Just a few comments about the complexities of this sort of population assessment. There's a variety of research approaches that might be appropriate. You can do a randomized controlled trial screening versus clinical diagnosis with outcome tracking. The problem always is ascertainment bias for kids who are identified clinically compared to those identified through a screening approach in which the screening approach will invariably detect more children on the milder end of the spectrum. So you have to have some way of detecting those kids and the Non-screening population. This Wisconsin CF trial is a great example of how this was done in a creative way years ago and I'm a strong supporter of that general design but understand that the ethical concerns around that may make it difficult and certainly not always appropriate for every condition. These trials are large. Long follow-up periods may be necessary, certainly true for the CF example the ethical issues as mentioned and always concerned about ascertainment by unscreened group. Next slide, please.

So a different sort of approach might be historical controls. I think we skipped one. Cohort analysis, comparison of screening in one or more states versus clinical diagnosis and comparable states. Neuroblastoma was an example of this sort of cohort design. You can perhaps include retrospective analysis of stored specimens in a similar population with outcome tracking as a way of trying to get around the ascertainment bias there as well. These are less able to be a randomized controlled trial but potentially fewer ethical concerns. Next slide, please.

Historical controls are always a possibility always fraught with difficulties when using historical controls but if you have a disease for which the natural history is very well characterized and you feel that that information is robust enough and sometimes historical controls can be appropriate. Do you want me to advance? Next slide, please.

Just a quick example of some of the challenges here. SMA study from NICHD, Kathy Saboda, from Utah is the PI on this and I am a co-investigator. Natural history reasonably well understood for SMA subtypes, -- muscle weakness and respiratory failure some promising pharmaceuticalagents coming along. So the secretary advisory committee had recommended a pilot study for SMA prior to making any further recommendations. This was an ambitious study. Next slide, please. Involving Utah and Colorado. They hope had been to recruit I believe about 400,000 kids with about 40 effected children identified over that period of time. There was a second add-on study that would have involved that -- that does involve early intervention for folks who separately consent to that intervention study. Unfortunately the study did receive support from newborn screening programs in both Colorado and Utah, but as the boots hit the ground on this we lost support from Colorado and then the Utah IRB required a full consent model essentially to conduct the study which has limited ability to recruit through the health system. So Kathy’s lined up a number of large hospitals in both states and the study is going forward but we have some significant concerns about whether the recruitments are going to be adequate to answer some of the key questions about SMA. So the point of offering this example is something to say that the state infrastructure that ended up being a challenge to support the study. Pretty much all the

other elements of an excellent study as far as we were concerned were lined up but we lost critical state support at a crucial period of time and that's the infrastructure want to talk about in this context is to say can we better develop that state infrastructure at the beginning or prior and have those states lined up and ready to assist the system in conducting this type of research who are experienced and available. Next slide, please.

I think I made this point already so next slide, please. The proposal really is a pretty high level sort of proposal here that I want to throw out for further discussion. What I'm thinking about is a multi-state network to support its population-based Phase 2 through Phase 4 research with my terminology, network of states familiar with and supportive of newborn screening research. IRBs within those states state systems that are familiar with the issues, state infrastructure that would be supported by federal funds in order to reduce the burden on the state systems for conducting this sort of work. And perhaps have an established organization to help coordinate the projects in this regard and a translational research network might be an excellent candidate for such an organization to support this type of network based pilot study. Next slide.

One of the advantages of this sort of system, generation of higher quality data is then available through the current haphazard system. We would be able to potentially recruit large populations and in a relatively short period of time make reasonably timely decisions on these issues and not have to wait for international data or data coming out of clinical programs. State pilots can be varied in selected ways to provide comparisons of elements of the system. Maybe different analytic platforms that might be appropriate in different states that you could compare. You could also of course do it as the neuroblastoma trial was done a number of years ago you where you would have one state that would be a control and others be the screened intervention. Network be response to recommendations organizations like ours, the discretionary advisory committee and presumably you would of course have a peer review system for the federal funding that would be involved here to make sure you had the highest quality proposals going forward. Next slide, please.

Disadvantages and challenges are substantial. Getting states to cooperate and buy in a to a uniform approach of course is challenging and that would be the point about prior discussions about these issues to see what level of comfort people had with certain study designs. The network participation may well burden newborn screening programs in a day and age when those programs are already burdened with just doing their daily job. Can we make a system that would provide enough resources to states so that it would not be an inordinate burden on those programs to conduct this sort of work? Families participating in network states would become research subjects on behalf of families in nonparticipating states really would become subjects on behalf of much of the globe's children so that it’s sort of an injustice issue if you have a couple of states that are doing all this pilot study is that fair and appropriate for families in those states if they’re a burden associated with that screening? On the other hand if they get access to more effective approaches earlier then of course it would be a big benefit to those kids’ families.

A network of a limited number of states may mean that investigators with disease expertise are remote from participating states. It is a little bit different design so if your rolled experts in Illinois and participating states are New York and California, how well does that sort of research work. Just a little different model than what has been typical in the past. –Conducting research may delay the adoption of screening modalities which may be beneficial. But if you force everything through a pilot study I think it might well but again there's always, you always learn something and in what you think you know it may not be what reflects the truth once the studies are conducted. I think that's my last slide. Let's check one more. That's where I want to leave it with my comments on the with the general notion that if we can do some detailed groundwork, try to get number of states and whether that's three, six, 12, 15, I don't know, large enough states to be able to answer some of these questions who have experience with this sort of work, who have IRBs that are familiar with the challenges that these sort of proposals involve and if you have leadership within those states that are supportive of being participants in this sort of pilot research network then I think you've got a long way to help establish the infrastructure that will be important for other resources when they come forward. NICHD has an RP that's been out now for just a couple of weeks about Pompe disease that's providing resources on a competitive basis to investigators who are interested in conducting screening. As I understand that RFB it includes researchers for the screening and the follow-up but not necessarily having pre-established infrastructure at the state level for doing that so this proposal would be in collaboration with that sort of screening opportunity to provide infrastructure would be essential to actually conduct the work in an efficient and knowledgeable fashion. I'm going to stop there and see if folks have any questions or comments for me and then would love to have more discussion and we will decide whether the discretionary advisory committee has a role moving this idea forward or not.

Joseph Bocchini:
Thank you Jeff very much. Let's open this for questions and discussion. So first I like to hear from committee members and then we will go from there. So Colleen and then Steve.

Colleen Boyle:
Thank you for sharing this, I think it is very timely that we consider this and I have one comment and two questions. One was the questions are -- I'm going back to Phase 1 Phase 2, Phase 3, do you see the primary intent on clinical utility just evaluating the clinical utility related to newborn screening, that's the first question. The second is early on in your presentation you talked about the importance of in terms of our evaluation by condition to be considered for the RUSP that there needs to be a population-based evaluation as part of that evidence-base and I thought we've had a fairly loose definition of what the population-based evaluation is so, I'd love for you to give some thought and comment to that. Then the last issue is I wanted to make you aware of something that was – I'm newly aware of and -- utilizing the network of the national Center on Birth Defects and Developmental Disabilities – in our CDC and our infectious disease world

there's an emerging infectious disease platform which is a nine state platform that involves academics and public health to really look at essentially -- the exact thing you are talking about. It is a platform that allows for ongoing surveillance and monitoring but then special studies within that context. We are tapping into that to actually try to look at some of our issues and it could be something that we can build on top of or even think about the model and exporting the models somehow.

Jeff Botkin:
Good. Thank you for those and I would say I think the utility would clearly be a major outcome of interest in this sort of study but it wouldn't be the only one. I think you'd be looking at test performance. I think you'd be looking at spectrum of disease. You would be looking at resource strategies for supporting effected kids and giving them access to the treatment modalities, bone marrow transplant and how does that work. In the real world sort of thing. I think all of those things would be part of the study. With respect to the definition I think the terminology here is important and what we call that it. Pilot. Talking about – Michael, I think earlier I think you identified that as a challenge where the field probably needs a better discussion of the terminology about what we mean. I guess what I mean is something that as closely mimics the real thing as newborn screening would be conducted in a clinical context if you can mirror that research context and I think your answering a lot of the real trench level questions that are relevant to making the decisions. I would not consider screening of anonymous dry blood spots even though it may be population level to be a pilot. I think you have to be dealing with identifiable kids and follow-up of those goods kits and assessment of their health status. I've not been aware of the infectious disease network. I guess there's probably a number of other good models out there that I don't know about. Maybe even the birth defects registry sort of thing might be other models where you have ongoing collaboration between states and federal agencies to help evaluate data on a longitudinal basis so that would be helpful to look at how that function but over the barriers and advantages and disadvantages.

Steve McDonough:
Thank you for an excellent presentation and also for advancing these ideas and I would hope that our committee would actually communicate these to the Secretary in some format, rather it be a resolution or whatever. I like to proceed to the next step. The questions I have would be how many pilot studies would you think could reasonably be conducted on it two or three period and do you have any idea what the dollar amount would be required or -- to do that?

Jeff Botkin:
I don't really have a good idea for the dollar amount. Obviously these studies are typically pretty expensive so maybe – Tiina might have a better idea of what the cost parameters might look like and I think that cost would probably be the limiting factor on how many you could do at any one particular time. Also if you had an uncommon condition and you needed the largest states participating then I'm guessing that would be a barrier as well as a lot of states could probably handle one of these at a time, but

would be reluctant to handle more than one. I'm guessing one to two would probably be the number that might be conducted at any one time.

Joseph Bocchini:
Let's get Tiina Urv to give us some additional information about NICHD in more of the data related to what's going on there. Tiina.

Tiina:
Hi, thank you. This is something we at the NICHD and NIH and her friends at CDC and HRSA have been thinking about for quite some time. Over two years ago when you do funding in the federal government you need to plan well in advance. So we thought we were planning well in advance several years ago when we put forward an initiative to develop a pool of states that as the need came up could be ready to step up and to pilot. And these would be states that had the ability to follow the kids and it was not states that could only do the deidentified blood spots but there they were actually the ones that could follow and refer their children and see the children progress through the pipeline so it would be an actual pilot of the newborn screening system. We learned a lot from SCID when we did this and we did this again collaboratively with HRSA and CDC and the different states that worked with us and we learned quite a bit. We put forward to our leadership at NIH to go forward to have such a group of states and we received approval and we were moving forward and we put forth last year a pre-solicitation notice that some of you might have seen that for groups of states that could look at a variety of different disorders. Then the sequester came and we were put off year so we are one year behind of where we would have liked to have been so we were on board with your way of thinking and we were happy to be ahead of the curve until they shut us back a year. But happily we were able to regain that year at the tail end of this. Some of you are in the process of working on solicitation for the Pompe disease contract which is modeled very much on this SCID and I cannot say a lot about that because it is an active competition right now. But we do expect to put out another pre-solicitation notice that describes the groupings. We felt it was better to go ahead with the Pompe because it was very timely right now considering that it was sitting and waiting for questions to be answered by a lot of people. We are moving forward in that way and we are again partnering with our friends from HRSA and CDC and we are open to suggestions when prior to the next pre-solicitation so we'd be happy to hear what you have to say.

Jeff Botkin: Maybe question back then, is there something that you think this committee can help in that process? Or are things moving along of their own energy at this point?

Tiina:
I cannot say anything off the record but if I did I would say you guys are doing a great thing, please don't take our money away again. So just a verbal support and just stamp of approval that this is a good direction to go in and if anyone has any other money that that like to add to it, we'd be happy to take it because we wrote the mechanism in such a way that money can be added.

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Joseph Bocchini: Pass the hat.

Tiina:
And partners are welcome.

Unidentified female:
Can I make a comment before you get rid of the microphone, Tiina? I do think that there might be a place for some of what you just bought up, Jeff in terms of defining a pilot and helping us to conceptualize the components that would be necessary. I mean I think obviously the government when they put together a solicitation for contract mechanism makes those decisions, but the input and the contributions of this committee obviously weigh in and help us formulate the solicitation so I think we appreciate your input and feedback into that process and is involving a moving target. Four years ago we weren't thinking along these lines but now we think of as a real necessity -- for conditions being nominated.

Tiina:
But move quickly because it is already the pipeline.

Joseph Bocchini:
Dieter?

Dieter Matern:
I have a question and again becomes a little bit it comes a little bit from the fact that I wonder about the role that this committee place and who cares on what we are doing. We recommended to the Secretary to include Pompe into the RUSP and we are waiting for a decision because the Secretary decided she wants to have other people look at this and see whether what we did is actually making any sense. Now NICHD is passing out money to do a screening study into Pompe or a pilot study into Pompe screening and I wonder why do we still need this when there's Missouri doing screening for Pompe already and we can just ask them how it is going and New York is working on this as well already.

Tiina:
I think SCID would be a good example of why we need to continue of getting larger states and larger numbers. How many births are in Missouri? 83,000 so when we did SCID we had defined find states of Massachusetts and Wisconsin and try as they might they could only have so many babies so when California and New York and Louisiana and Puerto Rico started participating we had a larger number in a shorter period of time. So what we're shooting for is as large a number of births as we can get in a short period of time to get -- instead of having the information dragging over time and it is not just the test and does the test work, Dieter; it is are these kids getting referred, do we know how it is happening, certain states can step things up and have the children move down

through the pipeline very efficiently, others cannot. People have different challenges so you cannot base all of your decisions on one or two states.

Dieter Matern:
When it's about follow-up however I think I know Americans are unique, but Taiwan in screening has been for Pompe for many years so one can get some information from them as well how that's going. So I just don't know why we are spending money for the same thing over and over again and I don't know why the Secretary would advise in July that Pompe should be added when she knows that someone made a decision within her department, I think, to fund another pilot study into Pompe.

Why would she say yes it add to it went up pilot study's being funded by the same place?

Tiina:
Thank you.

Jeff Botkin:I don't have an answer to that but I want to take a step back and say I think – the value of the pilot study is population based but it's primary value is to make an up or down decision about whether it on it to be added to the RUSP but there's secondary goals for that even if it looks like a valuable test to add, where are the weaknesses in the systems that need to be shored up so that the benefits can be maximized and the problems are downsized, minimized so there's a variety of data sets that are important to designing the best systems we can here above and beyond just whether it is a good idea.

Joseph Bocchini:
Joan and then Melissa

Joan Scott:
This actually relates to the question I was going to ask the committee about when in this decision-making process for considering the condition is when do you expect these studies to occur but there are different questions that need to be answered at different stages and Jeff you suggested that this is going to happen before decision was ever made to be added to the RUSP that but there's additional questions that need to be asked potentially after it so where in the decision-making process does this information need to be gathered? Is something nominated and then turf back and we say we don't have enough evidence on this and this and this so then we do the studies. Or do we try to project down the road and say how we do this before it is nominated, do we wait -- there's a lot of different stages there.

Jeff Botkin:
I'm not sure have a good answer to that. I would think that as the nomination process goes forward and as the committee begins to review data about a particular condition, if you had an established network of states who had been pulled into considering the

sorts of things there could be some initial dialogue at that stage. To say if they discuss discretionary advisory committee makes a recommendation for a pilot study, what would be your thoughts as a state and with you'd be willing to participate in that. That would provide feedback to the committee to say we've got folks ready and able to conduct this if we go forward with a pilot. If all of the states say forget it for whatever reason we are not interested in supporting that, then it becomes problematic for the committee to then say we need a pilot knowing that perhaps the system isn't prepared to conduct that. I would see an iterative process starting fairly early to see about feasibility that would help support decisions coming out of this committee.

Joseph Bocchini:
I'm going to address that little bit further Joan and I think that's a very important question and I think I'm going to propose that the committee to sort of expand on what Jeff just said about how we might use this sort of approach.

Unidentified female:I wanted to respond a little bit to Dieter's comments. I think the advantage to continuing to do pilot studies even on a condition that this committee had voted to add to the RUSP is that you help to add to the evidence-base that helps to support some of those issues about readiness and feasibility and some of the Phase 3 and 4 level questions which Jeff raised in his presentation so the purpose of doing a pilot is not just to provide information about whether or not something should be added to the RUSP but also helps us gather information about some of those post condition type questions.

Colleen Boyle:
I'm going to second what was just said because I'm looking at the Phase 3 and Phase 4 and obviously the economic analysis looking at the cost benefit – which was put aside here. Trying to weigh from a state feasibility perspective it's a state perspective and trying to balance the competing demends just for newborn screening but from the other arenas that -- I think that's really important -- and then what happens in the real world? We have this great promise of newborn screening but we don't have a good way of assessment how it rolls out afterwards so just having that as part of this network I think would be really the key.

Jeff Botkin:
I think what I have learned from Scott Gross over the years is the quality of cost-effectiveness analyses in this domain it is oftentimes poor in part because the studies have not been designed to begin with to collect the appropriate data that help support those sorts of analyses so if you're really anticipating looking at economic elements then hopefully the pilot can be designed to collect appropriate data so that part of it becomes helpful with the ultimate decisions.

Unidentified female:

I just want to comment I feel if you make the pilot study necessary before the nomination process it would inhibit people from making the nomination and filling out the form to nominate a condition but I don't think it should be a requirement beforehand.

Beth Tarini
The conversation seems to be touching on two separate issues based on the presentation one is this issue up by the study particularly about disorders that are upcoming or are already on the cusp of potentially being nominated. The second is where I thought you were going with this was the establishment of a consortium or network even if it be virtual like the NBSTRN like they've done for -- with a blood spots which you are doing. What doesn't necessarily go exactly with what you are talking about Tiina with your funding which is more to me building an infrastructure in which procedures such as IRB, data sharing, having states available to share clinical data if they are willing to participate as potential questions arise might be a useful place to start. My question then to the federal partners are there existing mechanisms built into structure for networks we could leverage and capitalize on currently?

Tiina:
That was the point of the NBSTRN actually.

Jeff Botkin:
Very well said from my perspective I think sounds right. And I don't know whether Mike wants to – I might encourage Mike to say something if he wishes.

Michael Watson:
So the SCID pilot was done through NBSTRN infrastructure for capturing data. Not so much -- some data came from states but other data required consent and states don't tend to get a consent so you are dealing with the diagnostic sector in capturing data to sort of the fairly broad system to get both state information, private provider information, some states contract with those providers and have that data, others it is a long process for them to get that loop closed on at least short-term follow-up. So I think the pieces are coming into place now.

Carol Greene:
[Indiscernible--Low volume] I think I should also say the SIMD, since I'm representing them has made efforts in the past to try to poll together that kind of consortium and have not really cannot until the NBSTRN as a place to go for support the – and the SIMD would be passionately interested and being a participant in any development of processes. To support this whole idea of improving information gathering to go with that said, -- I'm listening to incredibly good explanations of why we need to continue to do studies. Maybe [Indiscernible--Low volume] I think there's a language issue. Pilots are supposed be done before you're ready to adopt something and I'm hearing a beautiful defense of why we do more studies of Pompe but I'm hearing implantations studies. I think if you call something a pilot the states say whoa, we cannot do this, it still being piloted, it's still experimental, and I think the language might be important.

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Michael Watson:
The comment I was going to make relates to the fact that the fundamental the rare disease problem. I think if you look at other mechanisms where those problems had to be addressed at high levels you have things like the orphan drug act which fundamentally gives latitude to statistical power for a rare disease realizing that you cannot get the same power in short amount of time that you can get from or common situations so they overlay it with post-market surveillance which is a means by which you monitor the ongoing service or whatever it is to make sure it continues to perform the way you thought it was based on much more limited data. That seems to be the crux of the problem and what bothers the states is the mechanism whereby they can get involved in a pilot so it gets it on the list and then it is really hard to get off the list. So how do you get this sort of provisional category where it is investigational in place and then what is the committee really need to see data. I think could step back from a look at the incidence of conditions think how much -- how many patients do you need actually to be comfortable with your decision-making and that then tells you how many patients in the population are going to have to be screened to find whatever – the numbers always change once you start screening they become usually much more common than you thought they were. And the range of severity varies and that increases the number you need. I think that's probably where these post-market surveillance studies are very valuable is really getting you that population variability of the condition and other features of it that everybody's ultimately going to have to deal with in their screening programs and in the diagnostic side.

Joseph Bocchini:
Please identify yourself.

Ann Comeau:
I'm Ann Comeau from the University of Massachusetts and thank you for the presentation. I have a couple of comments. One as a state person, I have to say I'm very disappointed, Jeff, that with the presentation and from the committee also with the support that the states don't give data. The SCID pilot, the initial SCID pilot was two states who on their own came up with funds to study SCID and it wasn't just the test, it was putting together the system of SCID follow-up people. We shared those data with other groups. We shared those data with – Mae and I, people in our labs we shared how we did it. We shared the data and at which point it then became reasonable to say in order to get some statistical significance for rare disease it is reasonable to expand and go further. I'm just disappointed that the statement is taken oh states don't share data, states don't generate data, states don't give enough data. That's just not fair. You should take it back. [Laughter]. You should. There are several people here from the states who work hard to do this, not every state is a research state but that's not the purpose of newborn screening. The purpose of newborn screening is to provide a service and if we can build some research on top of that with some good protocols, well-designed protocols, fair and just peer review for what the protocols are, that's probably more important than having a very constricting and now I'm going to say some of that's

probably going to guarantee I don't get funding again, but a very constricting kind of talk-down this is how we are going to do it. There's a place for that, but there's also a place for innovation from the states to say “we think we can do this to go we are interested in this disease, we think we can do this, we think we can move this forward.” And yes, help from the feds is nice, but determination of how everything is going to be done to such a level that you have in order to do this you have to generate -- you have to participate in this, you have to give data here so that the real researchers can evaluate what you are doing is a problem. I think one of the underlying things here is a frustration that we all have which is that all of these studies require some long-term follow-up. And in order to determine clinical utility of newborn screening, you need to wait. You can screen kids and you are not going to know the long-term outcomes are for several years. It is a frustration but it’s a reality. So I think the idea of recognizing that some states do things on their own, that it would be nice if there were a variety of different funding mechanisms so that when states, when anyone has an idea of how to put something forward they can actually get funding without feeling like they are funneled into one thing and have to do it this way. Maybe in some situations it’s good to have networks and in other situations it is better to begin something slowly on your own and the network grows. When the network grows because there are people who want to work together and make it work it usually works better.

Jeff Botkin: Thank you. From my perspective, I think your criticism of my comments is well taken and always at risk if -- to suggest everybody has been functioning at less than adequate level. That shouldn't have been the implication of my comments. The system has greatly benefited from a number of states that have done outstanding quality research over the years. Massachusetts, Wisconsin, California, a number of states have been critical with their support and work in this particular domain. I think the point wasn't to say everybody's been doing a terrible job but rather simply relying on a few states to support the research and this whole domain is no longer adequate and we need a more robust system in order to support that and I do acknowledge the risk that there's a certain talk-down approach to that. That may be a price that is worth the benefits of getting good quality data that's consistent and [Indiscernible].

Nancy Green
Thank you. Thank you, Jeff, for the presentation and for addressing a number of important points. I was hoping that I can get you to speak a little more explicitly about the issue of consent in your terse recounting what sounds like a painful process. You suggested that the consenting would tip the balance against feasibility but there are other models. There are as you know; multiple models and I know you've thought about it so without giving you another talk, maybe can just make a comment about that?

Jeff Botkin:
Yeah, I think the studies that have been conducted over time have adopted a remarkable variety of consent models, some of them have been state mandates where it is simply added to the states platform and there's no additional or limited additional notification about the inclusion of that new condition on the panel. To others that have

tried to work through a full inform consent model and [Indiscernible] in California has done a bit about this and illustrated which I think is my experience but if you expect a signed consent approach to population-based screening the studies collapse. So newborn screening translational research network ethics and legal workgroup put out a paper this last year where we made an argument that in certain circumstances an opt out is the appropriate approach that enables families to be informed about it, but doesn't require a consenting model and I think that this is illustrated with the SMA study. Our work with families around this issue as part of the study clearly indicated that families want to know about these pilot tests. They want a choice but they don't feel they need to sign a form. That form signing aspect ends up being a serious barrier to conducting that. I think from my personal perspective if we get state programs to agree or IRBs to agree that this is an adequate way to obtain a form of consent and these certain contexts that would facilitate research. If states feel that a full consent model is necessary then either we've got to figure out how to do that in a more efficient fashion or those may be states that would not participate in the sorts of pilot studies.

Joseph Bocchini:
We will take one last comment and then we are going to have to move to the next presentation so if you will identify yourself.

[Indiscernible]:
Thank you, Jeff, and Nancy and just to expand on the position that I know you both also hold is it is obviously education and informed goes along with that so even if it is not signed there has to be the information given.

Jeff Botkin:
Thank you. I very much agree with that, certainly.

Joseph Bocchini:
Jeff, thank you very much and thank everybody for the comments that you've made and this discussion. Can we pull my slides up? I think some of the comments and the questions and responses have pre-staged this presentation so I can make it brief. I think in addition to the issues that Jeff has raised in terms of performance of pilot studies and getting adequate data we're really talking about pilot programs rather than a study. We are really looking at the entire program as to provide us with information about a condition being added to the RUSP. And can I have the next slide?

So this is our nomination form and we do ask in the nomination of a condition that a population-based pilot study be performed. However as we've looked at a number of nominations we've had some data that has been very limited, some data has come from other countries where the population may be somewhat different in terms of the condition being present. We've had some from states that are mandated by law to include the condition but again may not be for research purposes and as Ann pointed out we certainly have had benefits from states that have been innovative and initiated studies. But in essence, I think as we went through the evaluation of public health

impact it is pretty clear that we are not applying the pilot study data in the way -- the same way for every condition. That means we have gaps in some of the data. So what I thought based on Jeff's presentation and with this information and the efforts of the newborn screening translational research network that it would be a good opportunity for us to rethink what needs to be in a pilot study, what needs to be done in a pilot program at the nomination level. So that when a condition is nominated and have gone to the nomination [Indiscernible] committee that that be looked at very carefully and that we come up with some criteria on which to base whether we are able to move that forward or whether we should work with partners to try to get additional data. I think that this stage is set now for that to potentially be a way for us to go. So, my proposal for the committee was that we establish a workgroup with Jeff as the chair and then bring in partners from NICHD [Indiscernible] and NCC and others to really begin to look at this issue and to see if we can coordinate our efforts to try and in the end move things through more quickly and more effectively by having the data that we need to look at the condition. Based on the presentations I think the workgroups should have three goals. One would be to determine and recognize and support but the limited and so I think provide support this but report to the Secretary number one, recognizing and supporting the efforts that are already being made to establish a system whereby we could do this. Two, to identify resources or provide additional funding and other things and three, for our benefit to improve on the information that we need to get a condition nominated for the RUSP. Those are my thoughts. I'd like to hear any feedback from the committee concerning that.

Unidentified male:
I fully support that and [Indiscernible--Low volume]

Steve McDonough:
This is Steve McDonough, I'd like to echo support for that. And move a motion that the committee would support those recommendations.

Joseph Bocchini:
Any second for the motion?

Unidentified female:
[Indiscernible--Low volume]

Joseph Bocchini:
I'm sorry. The objectives would be to recognize and support the current efforts of the newborn screening network. To identify the resources that might be utilized for pilot program evaluation and to improve the information that the committee needs for inclusion in pilot studies for a nominated condition to move forward to the condition evidence review.

Colleen Boyle:

This is Colleen Boyle. So when you say improve the information you mean define what is the committee would require?

Joseph Bocchini:
Correct. Better said. Thank you. Peter?

Peter:
So um, to try to give an example yesterday we had proponents come forward and ask whether we could add [Indiscernible] synthesis to the panel so how what do we tell them, what do they need to do?

Joseph Bocchini:
I think right now they can go to our website and a look at the nomination packet and make sure that they meet the standards of the current nomination packet. What I ask is that we consider better defining what's needed in a pilot study so that when this comes forward to us as a nominated condition we have what we think is necessary to move it forward for evidence review. So if it doesn't have that then potentially we could utilize the relationship with the translational research network, other potential resources to get that data…help them get that data so it can move forward in a more expeditious fashion.

Dieter Matern:
I was looking for the last thing that we would be actually be helping them to get to that. Okay.

Joseph Bocchini:
Correct.
Part of the resolution is that the outcome of [Indiscernible] be sent to the Secretary.

Joseph Bocchini:
Right. At minimum we definitely want to support the efforts and encourage continued funding or maybe even better funding as we learn more [Indiscernible--Low volume]. All right. All those in favor, Aye?

Group Vote:
Aye. Okay. That will close that discussion. We now have public comments. We have three individuals who have indicated that they wish to make public comments. Our operator, is Garry Pyner, a parent advocate, on the line?

Operator:
He is Mr. Chairman and he's opening up his line as we speak.

Joseph Bocchini:
Okay, Mr. Pyner, go ahead and make your comments as yesterday each person who is making comments today has three minutes to speak. Please go forward.

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Mr. Pyner:
Thank you. I appreciate the chance to speak to this committee and I appreciate all that you're doing. I am a NICU parent and my son was born with and luckily quickly diagnosed with idiopathic pulmonary (Inaudible) in 1995. Today he's just completed his first year nursing school. But most importantly the ability of the -- to make a fast and accurate diagnosis which led to successful treatment. Today I'm asking for the groups' consideration in helping another group of newborns who are not as fortunate. These children are born with an inborn error of [Indiscernible] metabolism. This generic error results in a failure to thrive non absorption of fat soluble vitamins, bleeding, rickets and ultimately liver failure and death. In the United States this approximates 425 to 500 children born with this genetic defect each year. They often go undiagnosed for years as this alter or for orphan disease is a little-known. Luckily there's a subset of the 4 million live births each year that numbers approximately 20,000. This group of 20,000 is often diagnosed as having idiopathic neonatal [Indiscernible] stasis. It is of this group that I ask the committee to establish newborn screening for. And at the same time the North American Society for Pediatric Gastroenterology Hematology and Nutrition known as NASGAM [Indiscernible] is currently writing new guidelines for the evaluation of cholestatic jaundice [Indiscernible] in infants. Which in turn will touch on this inborn error [Indiscernible] metabolism. My feelings and timing couldn't be better to help these patients be diagnosed sooner because the quicker the diagnosis the better their outcome but also to help the families lead in a more normal quality of life with a child who is under excellent care and the prognosis is very good. I appreciate the groups' consideration and your time today. Thank you.

Joseph Bocchini:
Thank you for your comments Mr. Pyner. Yesterday we also had comments from Dr. Collins and another parent advocate concerning inborn errors [Indiscernible] metabolism [Indiscernible] suggest that advocate contact us to learn more about the nomination process and we are happy to encourage you to do that as well.

Mr. Pyner:
Appreciate the opportunity.

Joseph Bocchini:
Next is Amber Salzman, President of these stop ALD foundation. Amber, is she here?

Amber Salzman:
Chairman and members of the committee, my name is Dr. Amber Salzman. I lead the Stop ALD foundation. I come before you today in hope of accelerating the evaluation of the newborn screening for [Indiscernible] ALD and -- on getting transparency on the process. As you know at that January, 2014 meeting we were thrilled to gain the committee support for the full evidence review of ALD. Being mindful of the extensive resources and time required for a robust review, we were anxious to see the effort begin. As time marched on and additional ALD babies were born and put at risk without

a diagnosis I was informed that the committee has decided to re-examine the methodology used for the public health impact analysis portion of the conditional review process. Based on yesterday's discussion of this item it appears there is much work to be done here. This has put a delay in initiating the ALD effort. As we balance the need for strengthening this process with the need for a timely decision, I respectfully suggest that the ALD review begin and parallel with improving the public health impact analysis process. There are many facets to examine beyond the health impact and I respectfully recommend these activities progress in parallel. As you know, screening has begun in New York as of December, 2013 and to date, eight babies have been identified. With the newborn diagnosis their extended families were screened and additional lives were spared. Needless to say the families were beyond grateful for an early warning so they could save their child's life. In addition, the cost involved for caring for these individuals will be greatly reduced. With New York's success, other states are moving forward. We stand by to assist in accelerating the review so ALD babies not fortunate enough to be born in New York State may have a chance at a healthy and productive life. I would greatly value a timeline so I may update my stakeholders. Thanks for your time.

Joseph Bocchini:
Thank you for your comments, we appreciate them. And clearly our goal is to move as quickly as possible. We would be happy to discuss that with you. Next is Jana Monaco. Jana is a parent and former member of the committee.

Jana Monaco:
Thank you. For those of you who don't know me I am Jana Monaco. I am the advocacy liaison for on for the Organic Acidemia Association. I wear many hats within this advocacy efforts of mine. I'm actually a former member of the committee. Involved on the Council with NIMAC and also the Virginia Genetic Advisory Council and the chair of the – patient advisory committee at Children's National Medical Center. I've been coming to these meetings since the first is my very first one and happy to have only missed one in person meeting so I'm all about accountability. Over the 10 years since the very first one I attended a lot of the faces have changed, the work of this committee has been the same and there's a few familiar faces to it but a lot has changed. I am a mother of four children with [Indiscernible] and it is my two younger children. The reason I continue to be here though they have [Indiscernible] on the screening panel which I thought at the time once it was added my job was done. I learned that this is a much bigger project and picture for everyone. But how got to do this is because for those of you who don't realize that today is an important day for us, it 13 years today that Stephen had his crisis; that is my 16-year-old son for those who don't know. He was three years old and we had paramedics about this time 13 years ago we had paramedics at our house trying to figure out what was wrong with him. Take him to the hospital, transferred and he was in metabolic crisis. Unknown to the first hospital. 24 hours after his arrival he was in a coma, on life-support. Forty-eight hours after his arrival we received a diagnosis of Isovaleric Acidemia. Swelling on his brainstem and a very, very poor prognosis. Fortunately he survived with severe disabilities and complex medical issues-- it is a very long 13 years for him but his resilience has shown through

paved the way for his sister to be diagnosed one year later, of little surprise and she's doing remarkably well for an 11-year-old with her condition and facing typical everyday challenges. She's what you want for every one of these children affected. Through my years coming to you that I've noticed the conversations have been the same, the concerns have been very similar in the same but then it sounds like so long ago the issue was [Indiscernible] and how are going to add all these conditions and deal with them but back then states that already proven their ability to jump the gun and a look out out-of-the-box and some had already been added but unfortunately our state wasn't one was one of them otherwise Stephen would have been screened. As I say the conversations and concerns are the same whether its cost effectiveness, the numbers, there's not enough children, lack of staff, who's going to manage them, it remains the same but they found solutions when there were pushed to have to step up to the plate and add these conditions. As you are looking at these conditions coming through I don't envy you, I know the job of this committee is much harder than it was in the very early days and when I was on it. But at the same consequences still remain. Without the screening of these conditions, children are going to die or they are going to experience lives like Stephen does. And your work here can affect that outcome. I looked at the matrix box yesterday and I was a little concerned reading the A3s and A4s and the reasons and the prospects of what that meant so I caution you not to allow this really important vital tool that has served this committee very well over the years since its development, not to be used as an out, to not deal with these conditions because those may not be perfect solutions right now; the children don't go away, they still continue to appear somewhere in the medical system and someone has to address them. I encourage you to really try to help these states and these conditions by finding solutions to the barriers that exist. I'm really happy to hear about more and more studies and once again, states have proven themselves that they are going to go on with or without the blessing of this committee and whether there is screening or not and it might not be the most valued option for the government which is very, very slow, but I hope that you will utilize the information that they are gaining [Indiscernible] for studies yet get the data and its vital information that can be used to help develop it for everyone. I know cost effectiveness always comes up and I'm always very sensitive to that. One of the things that disturbed me the other day was hearing that our governments going to pay billions of dollars for a study on our twin astronauts to study the long-term exposure to gravity on the human body. It is a great study but it is millions of dollars and I thought if we have the money to do for something like that, there is funding somewhere to be found for vital issues like this and I think this committee as I said your role is difficult, your job is difficult, but you cannot push the envelope and look at it because the conditions are not going to be easy that come through from here on in, and I thought that was the biggest challenge 10 years ago. Don't be afraid to really rattle the chains in the government and really try to help them meet the -- find solutions to those barriers so that we don't have more Stephens and still have more kids like my daughter Caroline today. Thank you and thank you for the work you do and I'm really happy to continue working with you.

Joseph Bocchini:

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Jana, thank you for those comments. We appreciate them. We do have an opportunity to take a five minute break before we go into the next session so let's go ahead and take a five minute break. Everybody be back in their seats and we will restart. Thank you.

[The DACHDNC Webinar is on a break and will resume at approximately 10:30 a.m., ET.]

Joseph Bocchini:
Let's get started. That said can Lisa, can you pull up Dr. Watson's slides? Let's go to the next session. Dr. Watson, PhD, NMG–is the current Medical College medical genetics organizational representative to the committee. As of 2001 he became an Adjunct Professor of Pediatrics at Washington University School of Medicine and executive Director of the American College of Medical Genetics and Genomics, the ACMG -- ABACUS project director of the national coordination for Region genetics and new born screening collaborative groups and for the NIH, NICHD Newborn screening translational research network Coordinating center. He is also co-PI for the -- research -- resource project and NIH [Indiscernible] funded project to clinically annotate the gnome variation. He directed the HRSA funded project newborn screening toward a uniform screening panel and system. Dr. Watson received his MS in medical genetics and his PhD in physiology and biophysics at the University of Alabama in Birmingham while focusing on human medical genetics.

[Indiscernible]

Today he's going to talk to us about that new CPT codes established on molecular diagnostics and their impact on genetic testing laboratories and patient access. So Mike.

Michael Watson:
Thanks. I try to get Jeff to trade talks with me because I'd much rather do the pilot studies than this particular topic because this one is very hard. It is not something the committee talks about very often. Now am I controlling slides or is somebody else? I don't have any specific industry conflicts related to this issue outside of the fact that ACMG does represent medical geneticists and laboratory geneticists who obviously do a lot of this kind of testing and molecular diagnostics. Next slide, please.

I am going to try to zip through this because it is sometimes painful. There's some background things that one has to understand about billing reimbursement coverage policy, how rates and prices center on various healthcare services that ultimately feed into the process that we just went through that has caused enormous chaos across the country in the delivery of molecular diagnostic services in rare diseases. I'm going to go through that basics 101 and talk about some of the policy issues, work my way back through this process that's gone on for the last two years and is now in full chaos. Then

what we might need to do to figure out how to get a better handle on the processes that lead us into this problem. Next slide, please.

The coding systems, the fundamental issue that we are going to talk about is CPT coding because all of molecular diagnostics was given new CPT codes so to put these various systems into context, CPT is the way you describe what you did, no matter what the healthcare service is, laboratory test, whatever it is a it gets a current procedural terminology codes. That's assigned through the AMA's CPT editorial panel. CMS has a seat on the panel, Blue Cross Blue Shield has a seat on this panel. There are all specialties on this panel and it is a process by where they establish what an accepted service that deserves a CPT code is. The other part of the system is the international classification of diseases or ICD. This is how you describe what the patient had, what is the indication for the test. Many of the payers have linkages that if you have mental retardation or intellectual disability, developmental disability then this particular CPT code for [Indiscernible] a genetic study is justified so there are these linkages across the system but ICD is a much different entity in that it is not your specific comments international, WHO sponsors it. The U.S. has its own office I think.net CDC somewhere or certainly in Atlanta. It deals with ICD coding. It is been -- we are in a fight over ICD9 and the transition to 10. It used to change every five years and it is been a good 15 to 20 since we've got from ICD-9 or than ninth revision of ICD which has about 10,000 diagnostic codes to 10 that's going to have sixty-five thousand and there's huge resistance in the system for integrating that new change. Next slide, please.

So since we're talking largely about molecular diagnostics the CPT codes in that area get established and after one says that yes, the service is justified, it should get its own code the next step is deciding how are you going to figure out how to price that thing. The CMS does that and one of two ways. They either find something else that looks like that that's already being delivered as a service and they take that price and they crosswalk it to the new service.

That's basically what they referred to as cross walking. The other process is called gap fill and basically all that means is this something new, we haven't seen it before, therefore we need to do some sort of an assessment of this new test. Cost analysis, used to be the way it was done now it is more often than as almost as a negotiation between the individual laboratories that are billing the service, they get paid something and then they start interacting and saying that's not enough, it is not covering my cost of they go back and forth that way for a period of time until they come to some sort of compromise reimbursement rate. Next slide, please.

This is a much bigger system obviously the healthcare system in United States does not price everything the same way. You have private payers, we have Medicaid, we have Medicare and really what we're doing in this first stage is dealing with Medicare and their systems for pricing things. Coming down through starting the first decision was we're going to do a gap fill was the decision CMS mad that there was nothing you could crosswalk from. There was a real concern about what they referred to as transparency

of our coding. The system had been stacked codes that were largely methodology based you would code for a PCR reaction or code for using probes of various kinds but there was no Gene specificity to the system. So the payers didn't know exactly what was being done, they knew how we were doing what we doing, they did know exactly what was below that they were pushing hard for more transparency so they'd know what gene you are looking at and that's what they've done now but frankly that's not all -- it is good but it doesn't tell you which variance in the gene is the critical one you are looking at which is really what you want to know. I think the message here is if you look at Medicaid on this one side, many payers take their guidance from Medicare as to what the reimbursement rate ought to look like so it filters back through the system but it is complicated because the vast majority of genetic disease doesn't go through Medicare, tends to go the Medicaid because it is pediatric. They have a very limited history available to them and they are often saying why they are asking these questions. It is because they are the big dog who sets the rates ultimately whether they know what they are talking about or not. Next slide.

The other decision that has to be made is whether or not a new code is going to go on the clinical laboratory fee schedule, that's that fee schedule where CMS makes that decision between gap fill or cross walking, but there are many things in pathology and other areas of medicine where there's high complexity to the testing and to the interpretation of information that makes them decide that it is a physician service as opposed to a laboratory service. When -- the decision was when these new molecular codes came through the molecular pathology advisory group or the IMPAG up to the CPT panel the CPT panel accepted them and said this ought to be physician fee schedule, we think the tradition interpretation of molecular diagnostics is not so straightforward or well distributed knowledge that it should just be considered as a flat laboratory test. Where every physician knows with this result means. CMS decided no, that they were not going to place this on the physician fee schedule which has a very different way of determining rates by finding they ask a bunch of physicians who have expertise and experience in this particular new test and ask them to compare to other tests that are out there as to whether they think it is more or less work and that's how they come to a pricing on it. Ultimately CMS decided that they are going to leave this on the clinical lab fee schedule and there's lots of other issues that stem from that but I will spare you them. It does make it very difficult for organizations alike like ACMG and CAP and other professional organizations to deal with pricing issues because of antitrust law and price setting inclusion and all those things that you've got to avoid like the plague. It becomes a very vocal activity and we had to go through a period of educating all of our laboratory members to be able to do that local interaction the ultimately leads to how that pricing is going to be set with those local payers and the maximum Medicare advisory -- Medicare administrative contractors, there's a whole bunch of them around the country and we will see that in a minute. Next slide, please.

So coverage policy, this is the most cyclical thing I've had to watch for a long time. It goes from local decisions where local carriers decide whether something should be covered or not. Then they go through their rate setting to a national policy that was in

place 10 years ago where all the decisions about coverage were made nationally and they developed a new technology assessment program, all of which crashed and burned. Now they've reverted back to the local decision process which deals with all of the independent Medicare administrative contractors independently and Medicaid independently in each and every state. There are certain requirements on coverage policy that Congress has set that this local process has to specify under the circumstances under which the test is considered to be reasonable and necessary and that's the language used in legislation. You will see how the processes being used now are very different than sort of reasonable and medically necessary. They also require the contractor develop a new or revised local coverage decision policy when it identifies an item or service that's never covered under certain circumstances so for instant screening, Medicare doesn't pay for screening. Anything that is screening that they pay for is mandated by Congress so mammography screening, others of those kinds of screening things have to be legislated individually because Medicare pays for no screening at all. That's where a lot of our confusion came from in this new process is that we have in genetic testing we can do screening, we can do carriers screening, we can do diagnostic screening all at the exact same test and their understanding of which is the majority of testing and whether one is exclusive to a particular medication seems to have been some of limited. It is supposed be a public process where there's access to the Medicare administrative contractors and their medical directors for questions and their carrier advisory committees get involved in the process. It is very transparent and public and open which this has not been. Next slide, please.

When something is determined to be non-coverage and this is really an area where many of our current problems are coming from. There's two ways you could say something isn't going to be covered. You can either establish a statutory exclusion on it and fundamentally what that means administratively is that the statutory exclusion a matter how important that physician thinks that test might be for their patient or family they cannot even question the payer about it. The other is putting it in a category where they've excluded it pending determination of this medical necessity in reasonableness thing which enables the physician who's caring for the patient to engage with the Medical Director of the payer about their patient and explain why they think this is important to the patient. That's the -- so many of these new tests and the new codes of molecular were placed under statutory exclusion there isn't even the opportunity to have that medical necessity discussion available anymore. Next one please.

Now to the current process. In 1992 the first CPT codes for molecular were established. I actually was on the group of people that did it, that's because I'm that old. There were five codes, they would very basic about the methodologies used and that was all driven by the fact that CPT is a five digit coding system with very limited capacity for new codes. We knew that there was no way we actually thought that there was 100,000 genes at that time so we knew that told us the system wasn't going to work. Now we're down to 22,000 or so but the system still wouldn't accept a code for every single condition. So we stepped back and had expanded some of the methodology codes in 1997. Somewhere about '98 or so we added a two digit modifier to the back end of the

code that would say we were looking at this particular gene but an alpha numeric coding system gets you maybe of two digits. Gets you maybe 260 things tops. That's -- that obviously didn't have the capacity to last very long. The payers hated they wouldn't build it into the computer-assisted so it died of its own weight. Then in 2010 and when he '12 this is just about the pathologist begin an activity in activity to try to better define the molecular codes in a way that would give better transparency and a specificity to the type of gene that was being looked at. Still have the same problems though of a limited capacity the system to afford new codes to be introduced. So ultimately two tiers were established for codes. Next slide, please.

The first tier was the most common tests. That actually captures a good 85 to 90% of all molecular diagnostic testing that's done in the country. But it is only 100, 150 or so codes. All the other 2000 to 3000 genes in which we do testing today went up into the second tier of codes that's all defined by complexity. So rather than have to list every single one you can say that -- let me go to the next slide, please.

This is probably in bad order so I will say what I would've said before this. The basic if you think about tier two it's complexity-based so if you're looking at one axon of a gene by sequencing for instance, that's a very straightforward thing that many, many different tests might have in common. A single variant if you are looking - if you want to say that somebody's got sickle cell or the (Inaudible) globe and variant, one variant is all you have to look at in that particular gene. That's the most basic level one code then you come down through two to 10 variants in a gene, more than 10 then you get into lots and lots of sequencing of different size, numbers of axons in a gene, all of which is increasing complexity both of the analytical methodology but also the interpretation when you get into these more open kind of platforms what you take the information you get back rather than targeting a particular variant by a test. Those within two tiers and then the world went dark.

[Laughter]

Joan Scott:
I sympathize with you, Jeff. It seems some of the specific things in Tier 1 though meet the division of what's in Tier 2 like BRACA got lots of different periods and sequencing so why did some things get put into Tier 1 and not into Tier 2?

Michael Watson:
Because in Tier 1 it is all individually -- individual tests and there is not enough capacity for individual codes to that magnitude so what you begin to see is that Tier 2 there could be 20 or 30 different test under that first level one. There could be all the way through the there's a very large number of tests. Mostly for rare diseases where there's a very small number of tests done fourth -- of that particular test.

Unidentified male:

Are they meant to be used exclusively – you either choose Tier 1 or Tier 2 or are they supposed to be use (Inaudible).

Michael Watson:
They're supposed to be used independent so if there is a code for it in Tier 1 one that describes a test you are doing you are supposed to use that. And not revert to Tier 2. I won't go -- there's a lot of nuances and things you'd like. Tier 2 is probably the most informative place to sort out cost because it's complexity based and you'd like Tier 1 to align with Tier 2 but --

Unidentified male:
But if remember it really look like those were specific gene test almost for specific conditions. These are not diagnostic codes. We are talking about CPT codes so how do you guys think about that distinction? Because presumably the processes are similar if not the same depending on which individual gene you are looking for which condition you are looking for.

Michael Watson:
You try to align your test with your indication so if you're doing diagnostic test in the family you know their mutation our are variant that segregating in that family then you are going to fall into a level one targeted test presumably the least complex and least expensive. If you don't know and it is a diagnostic test then you may decide that there are 23 variants that are most common that you're going to target... If you don't see one of those, you will go to sequencing so you can think of Tiers within an area and in fact in Tier 2 we do have some -- in Tier 1 we have some variations where a particular gene is targeted and think that's CF so CF carrier screening under ACA that could be covered so it allows prevention to be covered but not under the current Medicare system. But the diagnostic applications of CF will go through a series of steps. You might look for the most common variants and target them, you don't find one of those then you go to full sequencing so there could be within a specific code a couple of sub codes that define the indication for the test.

Okay. Next slide, please. In 2012 the whole first wave of these new CPT codes got approved by the AMA and at the end of that year they go into the next manual of the CPT that lists all the codes that are going to be used by those people providing services. Next slide, please.

At that time --. That's hard to do. At that time CMS made its decision about all the stuff is going to go on clinical lab fee schedule and they are going to set the rates for them. Often upside down. [Laughter]. They made this decision between gap filling and cross walking. They then presumably described the methods that are going to be required and that was the all the Medicare administrative contractors around the country would have to be interacted with by the local laboratories to come to some level of compromise about what appropriate reimbursement looked like. They decided -- defined some of the parameters by which that happens. Next slide, please.

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We started late, how long do you want me to -- I'm going to try to zip if I can. 15 more minutes? We will try. So these are all of the Medicare advisory -- administrative contractors across the country that have to be dealt with individually at the local level by those laboratories that are in the states that are represented and these guys, it is like baseball. They trade players, they trade states, they get new contractors, it is a real moving target try to keep up with many of these go next slide, please.

Here we are, now we're in the current of what's gone over the last year. So in 2013 the codes were placed on the lab fee schedule and they engaged what has become the biggest gap fill process of all time. Typically gap fill is a single or couple of tests for which there's it is a new technology and the need to go through the process. They threw 200 and 20 or something into this process as a gap fill and imagine the rare diseases and the knowledge base of the medical directors of these administrative contractors was pretty tenuous. And most of them basically threw up their hands and just said we are completely overwhelmed. They had 6 months to do this so it is ultimately has led to the chaos. Next slide, please.

So part of the process has been arguing as I said you cannot talk about pricing antitrust issues and all that price setting stuff so you talk about cost. And you ask labs and tell you what does it cost to do you test? What is your reagents cost? What is your rent and all those other things that go to establishing cost? That is something that's developed after they established what they think it is going to be appropriate pricing so around May or so of 2013 this is just a handful of tests. This won't explode if I move the slide myself? Oh, good. Because my next slide is a problem. Because you cannot see anything. Is the same as this one so I'm going to go back and forth [Indiscernible--Low volume]. Molecular [Indiscernible] percentage and (Inaudible) arrays is down here in this second row. If you look at the way the pricing came out remarkably three of the payers came up to the exact same amount to the 14 cent line. Meaning that they talked to each other and all agreed about a price that might be applied to something. You see this in a number of areas and you also see a lot of not applicable meaning we are not going to pay for that, we don't think it is even a clinical service. They think these two carriers on the end of that was particular cytogenetic was research. You can see a number of these where they made that decision. They made any in areas that are really very complex where because Medicare doesn't pay for carrier screening it would look at CF and see the (Inaudible) of volume is carrier screening so what they basically took advantage of this opportunity to say we're going to revise our coverage policies independent of going through those congressional regulate mandated processes for coverage decision-making and they just said we didn't know that before so were not going to pay for that anymore. This has added a whole lot of the tests in the system.

Next slide. I won't show you many examples so we can move along. I'm not going to touch on this but the whole area of physician fee schedules versus lab fee schedules has implications for the different types of people who do interpretation and the majority of molecular diagnostic labs are directed by PhD's who don't to bill within the physician

fee scale list. That's determined by Congress under the Medicare Social Security Act as to who can bill for certain CPT codes if they are not a physician. So for the most part the people who are running the labs are trained to interpret the test are not allowed to a bill for the interpretation of the test.

Just as an example, the fragile X testing for FMR1, this is the statement. Palmetto is one of the Medicare contractors. They actually had a contract from Medicare to look at molecular diagnostics and they we're doing that for year or two ahead of time and much of what Palmetto, the unique thing about them is that the time he did this work they work two of the states under Palmetto were California and North Carolina so essentially Quest and LabCorp. So the vast majority of their data was coming from two very large national labs that had all kinds of capitated care agreement and all types of things for the way they price things out. They're hugely biased of what their cost was for many of these tests. So if you look at their statement now Palmetto has determined that fragile X testing is not Medicare covered service because screening in the absence of signs and symptoms of an illness or injury is not defined as a Medicare benefit. Now clearly these are not asymptomatic people. The statement becomes a bit absurd when you read through these things and there's tons of these. I did not post these coverage decisions to the Medicare website where all covered entities are listed. They actually were posting these as messages on their own websites and that was the only place you could find what was covered or not. So labs were running these tests for a long time and didn't whether they would get paid or not but they went through all the processing of tests. So lots of problems have stemmed from that because the profit margins in the academic labs are nothing to write home about. Next slide please.

How is this all playing out now? As we look at the range of decisions that are being made, as I said they're posting some of their coverage policy decisions on each one of the individual carrier's websites and their different so depending on how your patient is getting paid or could be very different answers. It might not be covered in one place or covered very low and another and as you see from that other -- table there are some things that are paid spectacularly well. In some place but way under cost in another test.

They are not putting them up on their coverage databases, they're getting around public policy setting in public comments, and the statutory exclusion problem is huge. We're arguing strongly that they need to get away from the statutory exclusion and put them into it least an area where medical discussions can take place between physicians and medical directors about medical necessity for their particular patient and that seems to be the model evolving where preauthorization is going to be involved for purchasing a molecular diagnostic tests, certainly those and cheer to unless they made a statutory exclusion. It's the base of disease probably had have -- we have had into that it's for long time. Put very non-very transparent process and if you look at the exclusions in the reason they did them, seven were because testing were being done asymptomatic people which Medicare doesn't pay for. They said it was used to. -- to cover diagnosis, other tests available, two were for clinical reasons that they would approve on a case-

by-case basis and an appeal of the tests. Six were because you could do both diagnosis with screening so they showed up – so they threw it out which threw out the diagnostic application at the same time and many argued there wasn't sufficient medical evidence which is not uncommon in the (Inaudible).

The immediate impact on labs has been that many tests were not priced initially. Most of the carriers were waiting for the dust to settle. We're in 2013 now and no price has been set by the carriers and labs are running and billing and not getting paid. I know one large reference lab billed $1 million to Medicare 2013 and at the end of the date they got paid less than $60,000 for all of that. Other labs and many labs have been closing. Signature Genomics closed one month or so ago largely because it was an unviable business route -- model at the rates that were being set for reimbursement. One of two genetic testing labs in Indiana closed. More and more are starting to line up and not just, not necessarily close but certainly not allowing patient access to something like a to know make it to race for autism spectrum disorder were clinical sensitivity is increased by 10% and they're going back to doing, they're going back to doing chromosome analysis which is what we're doing 10 or 15 years ago because they can get paid for that.

Next slide please.

As part of this cost setting thing we did some surveys and we actually didn't do it. We can -- we contacted and in December -- an independent consulting company to capture data from labs cost. This gives you a sense of how that played out for the rates themselves, actual costs is with the laboratories had submitted as their cost for providing the tests and then you can see what the gap fill rates and what the difference is and that is largely what we're seeing all across laboratory medicine is a 25% to 30% reduction in reimbursement rates and it's been a bit more severe in molecular diagnostics largely I think because of lack of understanding of the tests and the costs of doing them.

Next slide please. So, as I said, many of the carriers are considering hundreds of tests and tier two to be research tests and that -- for that reason they are excluding and preauthorization used to take place where genetic counselors might engage in the first line of arguing their patients for medical necessities. Payers now are saying the physician will have to talk to the medical director and if you have to -- if you have to preauthorize every test it's gotten up into the silly season pretty quickly and I've already talked about that last one. Next slide please.

Many labs are hanging on by the skin of their teeth right now trying to break even and not close down. It has huge implications. Many training places have to have a a molecular diagnostic laboratory to be qualified as a diagnostic training program as labs close programs are beginning to think about closing down as well. Next slide please.

Let's go through this one.

As I said, all the collateral damage from this is the payers revisited coverage policies independent by which coverage decisions should be made. Labs are beginning to close. Access to testing is probably the next wave we're going to see and that may be a place where the advisory committees may want to pay attention because it's really access to the services that becomes ultimately the most important feature of all of this and labs have been absorbing these losses and I mentioned the lab that billed 1 million and got paid $60,000 are not going to provide that test anymore. And it's a very precarious position to be in. If you go to court and you tell the plaintiff's lawyer that you didn't do this test because you weren't going to get paid for it you would just get incinerated for having made a business decision about the medical need for your patient. It's really causing a lot of problems around the country.

Next slide please.

Statutory exclusion is one of those spinoff areas that we are trying to get them to revisit. Medicaid is now starting to apply some of the Medicare coverage decisions and rate setting to their own policies and we're building a network of people in every state now to start interacting with the Medicaid departments. They have a very poor understanding of medical evidence around some of the decisions that are made and this whole area of national coverage decisions has become quite a mess.

I'm trying to pick up my pace a little. We said that already. Next slide please?

One more.

Here is where the disconnect is. There's always this area in the middle of the problems where the magic happens. In the eyes of Medicare and Medicaid right now the magic is really in what defines outcome. So we've had meetings with Medicare and the Medicaid part of Medicare and fundamentally what they said there was no inherent utility in getting a diagnosis of the condition. And then the next people went through period where they said they don't accept the diagnosis as having impacted outcome. Now I can show them based on knowing the diagnosis I ordered new imaging and other things known for that condition and that no longer has inherent utility what they want to see is if those two things change the outcome of the patient, which I can understand is an endpoint but it's very hard to get to in rare diseases if we don't capture the data far and wide it's hard to get the statistical power to answer that king of a question so registry systems are going to take time to build really allow people to aggregate this kind of data across 2,800 different genetic tests that are out there.

And then there is a secondary problem that's developing is another of the regulatory agencies and HHS's many Medicare, if it says it's an FDA approved test and they are good to go and go and they'll say it's -- covered and they will deal with pricing later. There are very, very few genetic tests that are FDA cleared at this point in time. Some what some of the carriers actually ended up saying is if you have an FDA cleared test

you don't have to bill it under the code and separate it out and pay you more than the FDA approved test all of which has impacted the laboratory test marketplace which is 95% of the markets or genetic testing services. So there are a lot of things happening that are sort of exacerbating the problem. Next slide please.

The last step of this was a law that signed by the president on April Fools' Day it's called Protecting Access to Medicare 2014 and fundamentally it was to fix the sustainable growth rate formula which is the SGR determines how reimbursement is going to increase over time to providers and it's been a real mess and something they know they had to fix but embedded in it is something that is to be one going to be of the significant changes since [Indiscernible] laboratories in the mid-80s, so it's going to define how billing codes are developed, it covers the coverage by which guideline policy, and price setting. What they're going to require a laboratory to do is actually affect incredibly granular level administratively is report back what every test was paid by every payer so that they can then identify the lowest payment and that will set the bar for testing because the goal is bring the cost of laboratory testing down by 75% by the year 2022. With 20 tests fundamentally being the target. CC is the most common test they want to get under control. But everything else is sort of getting captured in this so this is going to further exacerbate the problems of small labs and their ability to deliver services.

We have a lethal blow to rare disease diagnostic testing and lethal blow to innovation in small academic labs close up shop and we shift over to the big national lateral – and this whole local testing situations that are enormously valuable we don't have to send it to a national lab and wait for your results. We have that problem again, don't we? Well done.

As I said, there is a coalition of many professional organizations, largely laboratory oriented that's been negotiating and talking with carriers and payers about the problem.

Nest slide please

This whole MolDx program of genetic diagnostics which is what CMS has referred to it as have not thought – hasn't been following the requirements for coverage and price setting and not beneficiaries are being denied services. The whole idea of reasonable and necessary have gone out with the statutory exclusions. Next slide please.

I am not going to read all these. These are really recommendations we made to Medicare and that is probably not at the direct interest of this group. Next two slides please. You can read the kind of recommendations we're making. What does the committee like this have to think about? Clearly is access becoming a problem or not to testing that is considered medically necessary. Is there value in diagnosis of rare diseases because the data about the diagnostic Odyssey and it's costs are not trivial and it's these rare disease patients who go into the diagnostic Odyssey which can be incredibly expensive as they seek that diagnosis and now to get to the diagnosis, there is a whole number of other bars that have to be cleared. So I think that whole area of

rare disease testing; there are models like the Orphan Drug Act that recognize the problems of rare diseases. There may be mechanisms that can protect rare disease testing in the same way, rare disease therapeutics have been protected under the Orphan Drug Act and then looking at alternative approaches because I think fundamentally the top coverage decisions are made that is the problem is not well understood at CMS. They have actually asked directly for help on models on how coverage decision should be made on these rare genetic diseases that would help them work their way on what's appropriate in molecular diagnostics.

Joseph Bocchini:
Thank you, Mike. So you do have dialogue with CMS at the present time that but potentially relieve some of this?

Michael Watson:
We did talk to CMS but it does not get you anywhere because they don't pay directly for most of the genetic testing. If you look at side of genomic arrays the highest volume area of testing is intellectual disability, developmental disability, autism, spectrum disorder, pediatric conditions went back through Medicaid and Medicaid is accepting Medicare sort of pro-visas and now we're building this network to talk to every Medicaid department individually in the first two, Wisconsin Oklahoma have actually put in some changes and also just have made both that have really focused on pre-authorizations. It removes statutory but it's ridiculously time-consuming think for something of high volume as genetics or neurology type of environment for genetic testing.

Joseph Bocchini:
So do you think there is a role for this committee in supporting the efforts in some fashion?

Michael Watson:
Inheritable disorders of newborns and children, I think the whole access issue he has got to be important. As I said most of the labs have been absorbing be losses and are now closing. Others are shifting to older technologies that have less shifting technologies that have less clinical sensitivity. So the goal now is to find people who are being denied access to what is considered the standard of care service for whatever particular indication they have for their test. I understand whether -- understanding whether access is a problem or not is one of the primary areas of this kind of committee.

Joseph Bocchini:
Let's open up for questions from committee members first.

If there are none let's go to the liaisons Joan? You have a question.

-- Joan? Do you have a question?

Joan Scott:

I'll do it after.

Joseph Bocchini:
All right. [Laughter]

Let's go to Freddie and let's go outside to the liaison.

Freddie Chen:
Mike, the codes and the price list are all very much prededicated on a fee-for-service payment. As you know moving away from capitated systems as well as ACO's, how is that playing out in the lab world?

Michael Watson:
It is all adding to the chaos. You start with the US healthcare system and you've got just enormous variability. You have the ACA coming in that's dealing with 6% to 7% of the population, you got private payers, within the private payers is a wide range of what might be included in your plan. There are moves to try to rejigger the entire system around what you just said we've come in with a certain problem and for certain price based on your past history you will sort that out based on your past history of knowing what it takes across a population of patients with a particular presentation to get them to diagnosis and management but it's a long haul between them and we started at age really low bar place of knowledge and I think much of genetics just got caught up in this whole thing because the rare diseases or poorly understood. The Max couldn't keep up. It generated to the lowest common denominator and there was a great divide and conquer model when every individual lab has to do its own individual negotiation you have to negotiate with them about that whole reticular process.

Freddie Chen:
As much as getting caught up in the movement, things are not unrelated. The clinical utility arguments that payers related to the lack of evidence for X Y in genetics and see so now we are caught up in the value based pricing and higher efficiency and healthcare model. I submit that's not going away we need to be more thoughtful now creative. Paying the diagnostic odyssey doesn't compel payers.

Michael Watson:
It's not an argument but I don't think they understand its cost either yet

Freddie Chen:
I think that's fair. But I think obviously this work you are doing is so important, being thoughtful about how do you make this argument for value and how do you bundle an argument so that you can handle developmental delay and those kinds of things.

Michael Watson:
The other end of that spectrum is what they see as the ideal which is the companion diagnostic which is this therapy has been approved with this test. You do the test and

the test you're going to get particular therapeutic agent. There's very few of those in reality is we think it's how we manage this transition period and I am not arguing that we don't need to move and save money and healthcare. It's just not a hard stop and switch to a new system.

Joseph Bocchini:
We're going to do Joan and then we are here and in interest of time we're going to have to cut the discussions so that we can get to the committee meeting if that's okay.

Joan Scott:
Thanks for the presentation. It's beginning to lift the veil for me. There's a lot of history. I've heard about the concerns particularly around the evaluation of children with special health care, etc. What about access for concerns about access for the reproduction area. Is that also of concern?

Michael Watson:
In some areas yes. Doing amniocentesis and chromosome studies are still covered under whatever risk models you have that justify the test. Is the new preteting models in DNA drawing mother's blood and separating out those fragments of pre-fetal DNA that allow you to do a prenatal diagnosis in a noninvasive way that are getting caught up in this new wave because of the requirements. I mean most of those are being done mostly in a private laboratory environment so the clinical trial side of that is very different and so yes, there are problems on the female side or technologies.

Joseph Bocchini:
We are going to have to get to move quick.

Joan Scott:
We are having problems with routine carrier screenings. We are getting a lot of denials for cystic fibrosis routine carriers screening. That is the research base test.

I always thought our version of families was different than the physician version of families. Ours has huge risks associated in families of segregating variants that I think it's a very different kind of problem and clinical utility to families that's different than what is part of the system. The system is only focused on benefits to the individual who is receiving care and doesn't acknowledge a genetic family around that patient at the current time which I think is going to be problematic for having established clearly establish family.

Unidentified male:
Mike mentioned signature genomics which is a [Indiscernible] company or unfortunately I will use the word was. I worked at Signature Genomics half of my time last year and learned more about CMS and reimbursement than I ever wanted to understand. The big impact here I do not believe will be seen for couple years because what I think what this will do is and stifle research and innovation and new testing. Signature Genomics claim

that thing was micro arrays based on the posting on prenatal side. The day that will live in infamy as January 21st 2013 where those codes and Mike showed were assigned and if you know the world of CMS the day you get a the new CPT code reimbursement is zero and what you have to do is go through appeal processes you've got to go through making your case with CMS but the reality is that the costs because of the amount of time that is taken and testing, interpreting, resulting in ultimately reporting is very high, the infrastructure to report that is very high if you want to do a good job that that's I believe history will show that Signature did in fact do a relatively good job at that. That those costs were high -- but those costs were high. Mike alluded to it but we deal with CMS to get that kind off base rate in jewel notice that the costs were about 1300, the CMS reimbursement was about 650, the reality is the Blues and the Aetna say they're going to pay you 50% of the CMS rate so when you go to the Blues and Aetna for for reimbursement that is half of what you see there and after one year, and my job was to do operational efficiency and remove as much cost as I could but with the system set up you can't remove enough cost and it's totally a reimbursement issue. I believe and Mike and I have colleagues in the industry where those plants have shut down and they think this is critical and I think it will be more critical down the road were people realize this decision has stifled innovation. Thank you.

Michael Watson:
I was extremely superficial in my presentation. This is really nuance stuff because Congress often says whatever the Medicare system says the rate is you're going to get 70 percent of that rate so there's a whole bunch of over you -- overlays of reductions.

Joseph Bocchini:
Thank you for the very clear presentation and unfortunately there are significant issues that are going to have an impact over a long period of time so thank you.

Let's get one subcommittee report in before the lunch break. This is the laboratory standards and procedures subcommittee and I -- I think that Susan Tanksley we will begin this presentation on the telephone. Is that correct, Susan?

Yes. If they will be. Can you name? That yes. Ahead.

Susan Tanksley:
Thank you for allowing us to present our subcommittee report today. Kellie was been unable to join. I am giving the report out and Dieter will present his portion he gave yesterday at the end. We're going to hold questions to the end so we can get through this as quickly as possible.

We have three priorities for the lab standard subcommittee. Priority A is to review new enabling in disruptive technologies and for that we have her report on the succinylacetone implementation survey and that's the part that Dieter will be giving the summary of priority B to provide guidance for state news -- newborn screening codes and making implementations. We have an update today on the SCID slide project as

well as the timeliness of specimen transport and newborn screening and then our priority C is to establish process for review and revision of the RUSP and we don't have an update at this time but as we discussed the succinylacetone implementation survey yesterday we felt it might be a little cross cutting into Priority C as well. So just to give you and give you our subcommittee as well for ad hoc experts and again Kellie Kelm is the chair and I served as the chair with Tiina and Debi helping us out from HRSA. Next slide please. As I mentioned this gives SCID slide deck we do have a summary on that. We do have a presentation by Amy Brower correct this deck was built from worker discussions and that network consisted of Amy, Jane, Michelle, me, and Fred Lorey. The intent of this slide deck was to try to provide information that would be needed so that state labs or any lab who's considering and implement condition in this case SCID and they can discuss with legislators hospitals, stakeholders and basically what is needed when there and lamenting a new condition on the RUSP.

The concept is that an assortment of slides are provided and then the user can pick and choose the slides to use in their own presentation besides would be available to the states to use at their stakeholder presentations to provide information for them as well.

Next slide please

From the slides that were presented yesterday there was background on SCID that been added to the RUSP along with the [Indiscernible] federal partners in regards to state implementation tools and resources that were needed. There is a SCID monthly conference call and the vast majority of the states are participating on that conference call at this point. Ongoing efforts that are there as well as some of the publications. There was quite a bit of discussion about things that could be added. Some of the changes so there was talk about adding other references referencing some of the work that was done through those initial CDC grants, cooperative agreements to Wisconsin and Massachusetts and states they were working with and adding information on the algorithms for screening them etc.

The subcommittee but -- intends to provide feedback to Amy and the network group so that those changes can be made so this can be really valuable for the states who are still trying to add SCID. Ongoing, this would serve as a template as conditions are added to the recommended uniform screening panel so that information can be the -- be provided and conditions that are added to the RUSP. We then discussed the timeliness of newborn screening so as a reminder-- there was a public comment made – at the September 2013 meeting of the Discretionary Advisory Committee and it raised the issue of timely newborn screening and at that time the advisory committee decided to review the current policies and practices relating to timeliness in newborn screening in the US. Newborn screening has to occur in a timely manner and in order to effectively reduce mortality and morbidity. At the January meeting we had some updates. Next slide please.

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There was an initial survey done by the Association of Public Health laboratories. We reviewed some of the pertinent literature and looked at some of the previous discussions that had been held with the Joint Commission as well. At the January 2014 meeting there were four recommendations that the advisory committee made in regards to the time frames related to newborn screening and those are listed on this slide. First, that initial specimen should be collected between 24 to 48 hours of life. Second, newborn screening specimens should be received at the laboratory within 24 hours of collection, third, newborn screening results for time critical conditions should be available within five days of life and finally all newborn screening results should be available within five days of collection. Next slide please.

The lab subcommittee was tasked in order to review those recommendations the subcommittee was tasked with outlining newborn screening systems. What exactly is the newborn scanning system and what are the processes involved in newborn screening? Secondly to investigate existing gaps and barriers in newborn screening systems and third to identify best practices to achieving goals set forth by those recommendations, fourth to develop a list of critical conditions that require urgent follow-up. So if you recall the third recommendation refers to a call out of urgent conditions within the first 5 days of life. Fifth, to review technologies and suggest revisions if they are needed. Next slide, please.

This is a slide that I've used for several years and trying to explain who all the partners are and what all is involved in newborn screening systems and the part in the middle…so the babies at the middle… in the part in blue really in Texas represents what the newborn screening program is and what are the different components of the newborn screening program. However if you look outside of that bubble then it is all the other stakeholders involved in the newborn screening system. It's more than just the hospitals and primary care providers and the specialists who are caring for them. But it's all those other components that have an impact on the system policymakers, payers, regulatory bodies all of those components have an impact on the newborn screening system. When you think of in newborn screening as a granular process and what all is involved in newborn screening and so you may not be able to read all of these but it starts there are three phases of screening, there's the pre-analytical processes so when the infant is born, after the infant is born the specimen born the specimens collected it has to be to be transported to the lab, it has to be received, for testing, actually tested, the results have to be verified and reported and that is always been the analytical phase and it moves to post analytical phase with the steps of the reporting and the reports out physician have to be notified and parents have to be notified and action is taken when there is an is out of range result, there's follow-up done with the patient, diagnostic testing, treatment, and ultimately you have the long-term care and treatment of the child.

Next slide please.

All of those different steps can be measured -- all of the steps can be measured but it is very difficult to have process in place to be able to measure and capture that data in a way that it can be computed easy. So what has the Lab subcommittee been doing since the January meeting? We have been working very hard. We have a small workgroup. We call it the timeliness workgroup that has been recruited. That work crew did that involves Dieter Matern, (Inaudible) Mae Baker, George Dizikis Michelle Caggana; Ed McCabe has been added recently. Kellie, myself and we have a large group from the Association of Public Health Laboratories who are helping with this effort. We've been meeting every other week it seems like months at this point. We recently submitted an abstract for the upcoming APHL newborn screening and genetic symposium which will be held October 27 through the 30th in Anaheim, California this year. The purpose of submitting that abstract is we want to share the outcomes of the discoveries we made of the recommendations, best practices, the gaps, the barriers, etc. Our goal is to have a final product to provide to the advisory committee for the September meeting. We are in a very short timeline in producing a draft document for the committee for that September meeting. The Society of Inherited Metabolic Disorders took the issue of reporting of critical conditions on and we thank them for that. That group is being led by Doctor Debbie Friedenberg. That workgroup is assessing the metabolic disorders that they feel has the most urgent timeline screening for result reporting and we will talk in a few minutes of how what we're thinking about and how we handle the other conditions that are non-metabolic. We've also begun working with the Association of Public Health Labs to generate a survey that would have and accompanying webinar to gather gaps and barriers of best practices for timely screening. In several different settings at this point members of the workgroup have had discussions with either regional collaboratives. So I know that's happened with the Heartland regional collaboratives, with NIMAC with region 4and also with mountain states where various workgroup members have had discussions with their newborn screening groups within the regional collaboratives and have tried to begin gathering this information. What are the issues within your newborn screening system that would prevent you or do prevent you from meeting these recommended time frames. What are some of the best practices? What re some of the things you've done or could be done to improve the timeliness of newborn screening? However that takes a tremendous amount of time when you meet one-on-one or via phone call but when you meet together the information it does take a lot of time so we are trying to figure out a way to gather information from any newborn screening programs and other systems stakeholders would like to contribute to the effort so that we can have a more complete document and something that truly addresses gaps and barriers in newborn screening systems.

What are our next steps? As I mentioned, we are going to be -- we're developing that survey. We also want to have a follow-up webinar to that so that we have the survey, we send it out, allow states and other stakeholders to look at it but then have the webinar to go through the questions to make sure the questions are understood so that sometimes when you read a survey you read a question very differently than what the intent was. So the hope is that we can clarify those issues through having those

conversations and being able to answer any questions at that point. For those that are able to attend one of the webinars than we would hope to follow that up with some frequently asked questions that we don't put on a website that could be referred to.

One the questions we asked yesterday is besides newborn screening programs, so laboratories and follow-up staff, who else should participate in the survey? Some of the stakeholders we discussed yesterday were hospitals themselves. If hospitals are those collecting the initial newborn screen, perhaps we need to get them involved in the process and we talked about the process of the possibility of working on the March of Dimes consortium and The American Hospital Association engaging them to see if they would be willing to send this survey out to their membership. We are on a very tight timeline. We have to develop the survey, put it out there, gather the information it then compile that all within this timeframe of the goal that may be able to present the goal at this step tempered meeting of the advisory committee. We also mentioned possibly utilizing genetic counselors as another group of stakeholders to involve in the survey process.

Again, I mentioned that the SIP is the workgroup that is looking at urgent follow-up for the non-metabolic conditions and we're also trying to determine how we gather information for the non-metabolic conditions. We talked about using the ACMG act sheets and going through that process on some of them such as CAH, there's a requirement for urgent follow-up so we talked about the possibility of going through that process we talked about engaging groups of specialists be again to review those conditions briefly and just provide their expert condition as to whether that condition requires urgent follow-up or not. Next slide please

Again, our goal is to have our draft report to the committee for the September 14 meeting.

Now I'm going to turn it over to Dieter. Dieter, are you available?

Dieter Matern:
I'm here.

Susan Tanksley:
Thanks.

Dieter Matern:
I will talk about screening succinylacetone or rather screening for tyrosinemia type 1 which is been on the recommended screening panel from the beginning. At that time it was already pretty clear that tyrosine is not the best marker but the more appropriate marker to identify patients with tyrosinemia type one would be succinylacetone which is only elevated with tyrosinemia type 1. The problem is that not all of the used assays are actually detecting succinylacetone so some work is required. The good news at least on paper is that 50 or 51 newborn screening programs officially screen for tyrosine

type one and somewhat more concerning issue is of those 50 programs that screened sour tyrosine type 1. 38 only use succinylacetone. However I was actually quite positively surprised that some use Succinylacetone. The methods in the US used to look for Succinylacetone and dried blood spots are [Indiscernible] they are and these are laboratory based tests validated by each of the user labs but they are not FDA approved. There are two varieties. One uses the derivatization and the other one does not. And then there's a neobased non-derivatized kit where you can measure Succinylacetone. However, that has poor extraction for Succinlacetoone. But it is an FDA approved kit. So the concerns are on the one hand of course and it's not listed here that newborn screening programs that say they screen for tyrosinemia type 1,)in actuality they are not. And they will either miss a bunch of cases or will have a ton of false positives when they lower their tyrosine cut off too much. Then there are states that have to use an FDA approved kit and then there is the perceived perception that the FDA approved kits is not working well. Is that however true?

Looking at data from the region four collaborative project with respect to improvement of (Inaudible) screening when you look at tyrosine and Succinylacetone as markers for tyrosinemia type one, on the left side you see the situation for tyrosine derivatization. And apparently there is significant overlap between the healthy population and the tyrosine levels; and those patients that have tyrosinemia but again would be missed if you only used tyrosine. That is independent if you derivatize or not. If you look at Succinylacetone on the right side, if you compare the succinylacetone levels in healthy population which are light gray bars to the disease range for Succinylacetone in tyrosinemia type one patients or the black bars you can see there's no overlap between controls independent of whether you derivatize or do not derivatize on but basically you're using the basic -- the perception that one that assays is not working properly is not substantiated based on these data. Next slide please.

In summary, and maybe just click a few times until you see the whole thing. We believe that tyrosinemia type one should remain on the panel. It is a significant condition where early treatment can make a significant difference in the life of these patients. If you screen them -- do not screen them and they identified clinically then these patients will still have the option of not necessarily needing a liver transplant immediately NTBS is not effective in those patients when their instituted when the patient is already symptomatic so we do want to catch these patients early on. We believe that Succinylacetone is currently the best marker to screen for tyrosinemia one, and is currently underlined here because that of course could change. I'm not aware of any other biomarker except for DNA that might be helpful but there are a lot of private mutations in the gene so unless we have the chance to sequence everyone fast and cheaply I think (Inaudible) is the only way today and in the near future is the only way to screen effectively for tyrosinenemia type one and it doesn't remember which existing assays you use you should it -- should identify these patients and have a few false positives and no false negatives. The CDC arrived on the assurance of quality control and proficiency testing for tyrosine anemia type one including Succinylacetone and the CDC conducted a number of surveys of new ones training laboratories that do and do

not screen for tyrosine anemia using Succinylacetone and again there our 13 or 51 programs that screen for tyrosinenemia type one with unreliable marker, tyrosine by do they do this? One, the perception that the FDA is not good enough to use Succinylacetone and of course the usual issues of money, space, staff, and equipment. Next to slide and again you might have to click several times. What are the next steps we discussed yesterday? Victor DeJesus from the CDC, others from the CDC and myself wrote a manuscript describing our findings that you will find in the briefing book and we would appreciate your comments. Once we have received those and I don't know if we can give you a deadline, we would like to submit this for publication so we would like that input from you the other issues is what should happen with the work that was done should our committee or the secretary recommend that Succinylacetone is a more appropriate marker for tyrosine anemia type one or should our committee acknowledge the value of the article in and article to the website and make it -- meet the states aware that this is out there and they can read up on it. Many of the subcommittee members also thought that maybe we can take special states -- steps to educate those screening programs that currently don't use Succinylacetone as a marker for tyrosine anemia type one screening. I think that is all we have. Next slide.

I guess that is the last one. I will open it for discussion.

Joseph Bocchini:
Thank you Dieter, thank you Susan for your presentations. Let's discuss the questions that Dieter has raised. Remember, in order to make the recommendation to the secretary we would have to have it posted prior to this meeting so that we would need a formal vote. On the other hand we could by consensus make the secretary aware that the committee has performed this review and then follow the rest of the -- the recommendations that you have made in terms of promulgating this information through APHL and other resources to make the states aware of the data review and the data that's available. Let's open this to the committee then for questions or discussions.

[Pause]

Unidentified male:
Thank you for really great presentation. I think the educational efforts if you get an opportunity to get the other 13 programs in line, if not something more rigorous do you think that would be a workable we of doing it? Here?

Dieter Matern:
The CDC, as Victor told us yesterday, has the opportunity to educate screening laboratories on a regular basis. I don't know Victor wants to -- comment on this for all of us but apparently it has not worked for 13 programs. I don't know of 13 programs means 13 laboratories. It could be one laboratory that serves 15 states. I know Massachusetts does that they were one they were one of the first to do it and they cover five states total so that doesn't leave too many others to cover other states.

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Unidentified male:
Perhaps I missed it. Are there specific barriers for states to make the transition from tyrosine to Succinylacetone? I mean do they recognize that this is an issue or are they not able to do it for some particular reason?

Dieter Matern:
I will let Victor answer that.

Victor DeJesus:
CDC. From our survey several barriers came up. As [Indiscernible] mentioned the presentation, cookie-cutter, lack of funding for it, lack of space, new implementation, we have for several years operated the program for Succinylacetone interrupted time we have been working with many of these programs to help implementation. We have unfortunately very little to do with such decisions at the state level. I don't think that implanting SUAC at the state level it really an issue. It has to do with funding and the wherewithal of those involved in those decisions. Again we can make recommendations from CDC but it is still a local activity. I think everybody at least from my experience with my conversations with the labs, everybody realizes that Succinylacetone would be the preferred marker. I don't think anybody doubts that for one minute. Again, there are many, many barriers and these are the ones that are communicated to us. The surveys were self-reporting so we're just communicating what we heard and from personal conversations it echoes for what I've been hearing for many years now from all of these labs.

[Indiscernible - low audio]

I'm sorry?

[Indiscernible - low audio]

Victor De Jesus:
I'm going to go to Mae here –

Mei Baker:
(Indiscernible) heavy accent…here the whole aspect here is the buildup of multi-flex so when [Indiscernible - heavy accent] is a part of that. Succinylacetone…of course you have a lot of things you can do. Extract together combined together but [Indiscernible - heavy accent] costs $400,000. You'll get additional equipment to do this assay. It's not trivial. I want people to know the background and you can imagine that Massachusetts, multiple spots [Indiscernible - heavy accent] when you found (indiscernible). We have to do separate and we use like three spots combined together and you said are caught off. You have to do this injection overnight. [Indiscernible - heavy accent] there is difficulty in funding results.

Victor De Jesus:

You also have laboratories currently using derivatized (Inaudible) kit who have evaluated the new kit and found issues with it that they have decided not to make the transition and their constricted to use FDA kits (indiscernible).

Unidentified male
I just wanted to say as Dieter or told us more comments and feedback from the subcommittee yesterday and there is this misperception on the part of some of these labs that the non-derivative kit does not work well and Victor's data shows that's not true. Somehow that message has to get across because they are using some -- some of the labs are using that for the reason that based on incorrect information while the correct information is available.

Joseph Bocchini:
Comments? Questions? Recommendations to the full committee?

Susan Tanksley:
We did an informal vote just to find out each person's preference on the subcommittee and the subcommittee, really most people work adjusted in trying to work on this to the educational opportunities so APHL has multiple committees but that QAQC subcommittee could intentionally take this up in they do webinars each year and possibly it could be the focus of a webinar which is broadcast available with all the states. That's one way. With new steps there our site evaluations and so that could potentially be worked into the evaluation towards. Are you screening for tyrosinenemia type one, if so, how are you screening? There are different ways. There is also Kindle mass courses that are caught in that could become a focus within those courses as well for screening for tyrosine anemia as well. That is what will we talk about the subcommittee there were some that wanted to come to you, the advisory committee and get your opinion on whether it should go to the secretary or whether we should focus that via the of that educational route instead.

Joseph Bocchini:
Thank you, Susan. Any additional comments from the committee members?
Jeff?

Jeff Botkin:
I certainly like the notion if of you screening for this disease to go from what looks like and ineffective or inappropriate test to one that's highly effective. It doesn't sound to me like the issue is as much education but maybe non-derivatized is not an education but it sounds like it is kit fees. Programs weren't doing this and it sounds like they have to increase kit fees to make a transition to the new Succinylacetone approach and we need to know little bit more about that before making a recommendation or raising that issue about whether we might need more information about trying to understand what the public health system impact might be on the recommending on testing approach?

Dieter Matern:

This is Dieter. I think given that most of the laboratories are already using Succinylacetone and working in the lab that has made the switch and others can't speak to the two I don't think it was expensive to add Succinylacetone to the screen. I appreciate that if you do the structural acetone separate -- the Succinylacetone that you double your instrument time. Most labs to simultaneously so it doesn't really add a lot of cost it at least that's my experience. We use that dangerous hydrazine for the Succinylacetone derivatization and we modify it for $500 our autosampler by basically putting a hood on top of it and that was it and the regent costs that are minimal but are going up.

Joseph Bocchini:
Alight. Other comments? If not may I suggest that we accept the report from the subcommittee and that they go forward with educational opportunities that would put on the agenda for both -- a vote in September of whether to send it for formal recommendation to the secretary? Is there general agreement with that? That sound like a general agreement with that?

I'm sorry?

Now to move forward with the education now and then put on the agenda for September e full committee vote on whether to send this as a formal recommendation to the secretary.

Dieter Matern:
Dieter again that does not preclude us from publishing the manuscript? Good.

Joseph Bocchini:
Correct. It does not expect and my acceptance by the committee that means you can go forward with that publication. Any concerns with that? If not, just signify agreement by raising your hand. Okay. Unanimous. We've gotten a little bit behind. For the comments, (Inaudible)

Dieter Matern:
We still have the other timeliness of any questions about that?

Joseph Bocchini:
Any additional questions concerning Susan's initial reports and the rest of the activities of the committee? Subcommittee?

Colleen Boyle:
This is Colleen. Susan, thank you very much in the committee member's thank you very much for such a thorough examination of this issue. I'm pleading ignorance here but I was wondering if there our performance measures or if you have thought about considering performance measures as part of the way of perhaps standardizing the approach to the timeliness issue?

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Susan Tanksley:
With new steps, their quality indicators that have been proposed and definitely timeliness of the large segment of the quality indicators that have been proposed. Measuring different parts of the process so that would definitely be an ongoing thing. As far as collecting the data now. If you recall from the January meeting there was a presentation by APHL and they did try to collect a lot of that information for that presentation but unfortunately a large number of the states were able to provide the data in uniform we so we could all be aggregated together and compared so I don't know if we will be able to get enough data in the short timeframe to really show what our baseline is right now in every state. We may be able to get that sort of data from a few states and be then able to present it and say okay here is a sampling. But we also need to figure out, in addition to what is the baseline, what are the issues that keep you from meeting these time frames. There are substantial barriers. In some places we have heard already, for example, lack of courier in large portions of Alaska. Complete lack of courier it seemed issues abound in Hawaii. There are things that are substantial barriers and then there are also l things that are daily work processes and are things and it's the way we do it and that's the way we've always done it and sometimes rearranging those things when we look at it in a different light and was a different angle in mind that we can make simple changes and sometimes make a big impact as well. We're trying to investigate all of those things and hope to report on that as part of that September report along with best practices and then the barriers, those things that are really substantial and stand in the way of progress so those can potentially set forth and work on things that we are trying to eliminate. So yes, the quality indicators it definitely something, performance measures are definitely something that we hope will be put in place and I mentioned in my presentation that there are all those different steps along the way that you can measure but you have to have a weight to collect that data in a way that makes it easily computable. If you can't collect the information in a way that's easily query able, it is very difficult to compute those timeliness statistics. That is something that moving forth would be encouraged is the best practice is to be able to capture those time points so that you can actually analyze and have real data to look at in the form of performance measures. Does that answer your question?

Colleen Boyle:
Yes. More to come, right?

Susan Tanksley:
Right.

I think in the interest of the lunch we have brief, less than a minute. That's okay.

Unidentified female:
Just to continue with what Susan said we do have quality indicators and that is by the newborn (Indiscernible) community and I don't know whether statement from this committee could help to put pressure on the states but help to encourage that in terms

of data into the system. Many of tm are already to our memorandum understanding, could they get the performance measures entered earlier and available for your information.

Joseph Bocchini:
Certainly if you would like help from the committee we'd be happy to provide it.

Unidentified female:
Okay.

Joseph Bocchini:
Let's go ahead now and break for lunch but Susan and Dieter thank you very much and thank you to the subcommittee for continued work. Since we're starting the lunch break -- lunch break at 12:15 let's get back probably at 12:45 p.m. so we can get back on track so people who have to get airplanes can get them. Thank you. We will meet again at 12:45 p.m.

[Event on 30 minute lunch break. Will return promptly at 12:45 p.m. EST]

[Captioners transitioning -- please stand by]

Joseph Bocchini:
We appear to have a quorum so let's go and get started. We will take role.

[Roll call]

(Roll call)
Joseph Bocchini:
I think we are ready to begin. We are now going to have the report from the follow-up and treatment subcommittee and I want – (Indiscernible) at the beginning of this meeting. Carol Greene [Indiscernible] by after this meeting [Indiscernible] which she very quickly reminded me of -- my mistake the again, again, thank you for all the work you do and the best to for committee so I'm going to turn this over to you. And get started.

Carol Greene:
Okay. It is my pleasure to do this report on behalf of Chris Kus who actually lead our meeting yesterday but could not be here today and Charlie Homer with whom the planned some of the discussion but could not be here today. So I'm going to give you a very quick review of the charge and priorities that the committee has given you the sub-committee which hasn't changed. A review of the work since the last meeting and most of the time we hope to spend on discussion of the document that was submitted to the committee for review that we would -- we very much hope to move forward on publication. It's been in progress for about a year and a half since the committee tasked us with this and then to spend a couple minutes on presentation to the committee of

possible future projects. Just to remind you there's our roster. Our charge as it had been revised in 2011 and a looking at barriers to implementation of sure and long-term follow-up including treatment, recommendations for overcoming those barriers and guidance on responsibility. That was the subcommittee charge.

Within that charge, three priority areas were identified by the committee and within those areas as with all the subcommittees within those areas we were asked to undertake some projects. Priority A is implementation, priority B is closing gaps in care and priority C is impacts and outcomes. Spin I'm going to tell you that priority A, the project that was assigned has recently been completed and when I tell you in a moment what we've been doing since the last meeting I will not have to repeat that what we did this is because the manuscript was liked by the committee at the last meeting there were just some tale ends of things about to put in the final edits as recommended by the committee and the how it to go looking for publication. That is in process, but it is really the dissemination process at this point.

Priority B, I think you will see when we get to the very end and talk about what kinds of things the subcommittee would be interested to have the committee task the subcommittee to do will have to do with this priority B, closing gaps and systems of care and to do with understanding access.

Priority C is a project we're going the spend some time talking about today, the project was assigned to explore whether we can document improved outcomes after newborn screening and it evaluating how those impacts, how the outcomes relate to the various activities.

And specifically I will come back to that in a moment, in order to do this we've been having monthly conference calls and additional phone calls for a writing group, working on that priority C project which is called – (Inaudible) better outcomes for newborn screening, do we know if we are achieving the promise of newborn screening and to remind the committee we were asked to do this and to make very sure we would not duplicate other efforts at NHS or anywhere and our focus was to work on developing key questions and understanding data sources and understanding gaps in data that would allow us to know whether we are getting better outcomes as a result of having doing -- result of doing newborn screening. We were asked to create a framework which we actually have done before and have brought just remind you at the last committee meeting we brought the framework in a very early draft of paper but with a framework which is basically looks like a table and the committee had said we were on track so we went forward and have developed a manuscript go with the framework and added to the framework that started with sickle cell as the example and added PKU. So we were asked to create a framework which we have done to sickle cell as an example to test and develop that remark and revise that framework as needed in order to be sure that includes a central data types and permits mapping of data sources to understand the outcomes and identification of where there might be gaps in data. Then we were also to test and revise that framework using at least one other condition so we are sure that the

final for being able to apply to all the -- disorders. What we have now for you in the briefing book and it has to be the revised review book because something very distinct about the PDF process did something really creative to the title headings on the table in the first attempt to upload it for you guys. Debi give you a revised version. With that draft that you have starts with the basic framework in the manuscript as previously seen by this committee so hopefully we are still on track. We had some discussion about whether to stick with just sickle cell as a table as a framework example in the paper and we had quite as many of you to remember, quite a number of rounds but other people are getting the data for sickle cell and this is not an attempt, I want to be clear, it is not an attempt to gather any data. This is an attempt to create a framework that anybody, any state, any program can use to go looking for the outcomes and looking for where they will fund the different outcomes and evaluate whether or even is any data to look at the outcomes and we realized very quickly that if we also put the table for PKU in the paper it would be much more clear to people that this is about the framework, about the framework as a tool that you can use and not about a specific disorder. With that said, I'm sure that any of you who've already read this manuscript that we are about to discuss have realized that the PKU part of the paper, the PKU table doesn't look as finished as the sickle cell and that's because we got it in a hurry. So what we gave you to review is text that we are very happy with and I now have four at items from our meeting yesterday. But text we are very happy with the table is that still need a little bit of work but had been like in principle in the tables actually have to be cleaned up a little bit and the tables -- the one new element of the paper is called the driver diagram. I want to orient you to that and that was added since the last time the committee saw the draft added at the strong request of our experts in process and QI with the point being made that the tool, the framework looked terrific but it would be not usable by people attempting to not only assess whether the system is doing good, but also if it is not doing good enough to assess what changes should be made if it is not tried to something called a diver diagram. At driver diagram being a model that currently used and QI that allows people to look at what are the elements of a system that drive the outcomes. So we started with the framework we added the driver diagram and the last thing that we need to do to finish this manuscript will be to change some of the headings in the table to match the driver diagram is the driver diagram exactly matches the headings in the [Indiscernible] paper and the [Indiscernible] paper and that will just wrap it back around. We have a little bit of cleanup to do on the tables but the text is there for discussion. I should tell you that I only mentioned we have four edits to the text and I will be very interested to see I can either give you those four edits first or we could see whether those edits already address questions that the committee has about would you prefer I give you those four edits first? Or walk through the paper first?

Joseph Bocchini:
I think if they were minor edits.

Susan Tanksley:
They do not change the substance but they are not exactly minor, they clarify.

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Joseph Bocchini:
Okay [Indiscernible--Low volume] Then I think you should do the general…

Susan Tanksley:
Discussion first? Okay.

Joseph Bocchini:
Are there any specific questions or comments related to the draft that was put into your briefing book? Hearing none, I think that the best thing to do is to since we've been through this and you had some edits, if the committee will accept the draft, if you do make major changes and want to send it out again, that would be fine. But from now I think the same thing applies to the presentation that Dieter made I think from the last iteration you have two weeks to provide comments back, but as long as there's no major substance changes then I think the committee can accept this to for you to move forward with publication. If there's any issue that's been raised by the review of the paper? So I have a hand count on to accept the paper? And allow it to move forward? Seeing none, we can move forward.

Susan Tanksley:
Wonderful. I can walk through these next three slides very quickly – in the interim we are going to add white views use but the sickle cell and PKU endpoint out that it shows differences in types of diseases differences in data available. We are going to take out every record of the secondary drivers because many people found that confusing and wasn't in the table anyway. And just put in a little bit earlier in that paragraph that an explanation of what is the driver for a primary driver. The next page we are going to refer explicitly back to those papers they gave us the primary drivers for the diagram and do a little punctuation clean up and take out all references, secondary drivers and this is just to be added to the summary which there were some comments that the summary was nice and generic am looking forward but we didn't actually summarize what we think we did in the paper so this was language that the subcommittee agreed was appropriate for the summary. I don't think any of those are substantially, we look forward to comment from the committee and we will put those in and clean up the tables. The last two slides, Dr. Kus led us in a discussion of some ideas that have been gleaned from the subcommittee in the past and from some discussions that several of us had thinking about what might -- we are about to finish our second project so we finished our first -- finished our priority A project and we are about to finish our priority C project. Several different possible projects or ideas for projects were put forward. One would be to build off this framework manuscript to actually do a test run and see, pick a disorder, pick up a couple of disorders, use it, what might be used for QI. Another would be to explore the public health clinical interface and another would be to begin to build program improvement capacity. I should say that one comment on the building program improvement capacity was that it is kind of hard to talk to people about how to improve our program if you don't you understand with the program looks like and there was a lot of interest in moving forward with exploring this public health clinical interface, how the system it really relates to our priority C category and to begin to use the work that has

been done so far, the one we are just completing, the [Indiscernible] paper, the original paper about what is long-term follow-up and a specific proposal as described by to Dr. Cook for a possible future activity would be to describe the current public of clinical interface of what happens in the follow-up so we are not talking about the original screening but consider profiling and a possible way to do that would be to consider profiling several states on how does it work in the states how does public health system and the health system work in providing care for these -- for individuals with conditions picked up by newborn screening. There were some other ideas that were put forward. This is the one that Dr. Kus wants me to lay in front of the committee as a possible project and then see if there's other suggestions or ideas.

Joseph Bocchini:
Great, thank you. Actually there could be some overlap with this, with the planned evaluation of new conditions in the expanded public health impact evaluation so -- but I think having a better understanding overall of public health clinical care interface would be very helpful to the committee so I think that sounds like a way to go. Let's have some input from the committee related to that.

Joan Scott:
Would you consider this -- there's a number of different interfaces that are potential and one happens right after the diagnosis is confirmed and then you [Indiscernible] for care or another could be longer-term and how public health system a track children over time so would you consider all of those potential interfaces or one being more important or need further exploration to define?

Susan Tanksley:
I can tell you my sense is that we really were – it is my understanding that we are interested in the big picture of the whole system. Not just tracking, not just one point in time and not just one activity but looking at the big picture to try to better understand it. It would be more descriptive and a large part of the interest has to do with issues of access and also understanding the various roles and responsibilities. I don't know if that's a complete answer to your question but insofar as you gave two good examples of places you can look, one is a time related, the time of turning over and another one is specific function related is the tracking. We had no intent to narrow it down that way but to look at the whole complex interaction of the system.

Joan Scott:
In context of this public health and clinical care interface, under the closing gaps, I think there's two things that have been happening that directly impact access to care and that I think should be could be looked into. One is lots of access to specialty care to be such a benefit packages, they are not there and so we can look into that. Mainly due to the restructuring of the funding at the state level and so the impact of on access there. Then the second one which came up a little while ago in meetings I think two meetings ago, the reduction of readmission rates on the part of the Affordable Care Act that the impact beyond CF which has exclusion that of the other discernible disorders have that

exclusion and the potential for loss of access exists. For sickle cell disease specifically as an example that readmission rate when you are looking beyond 14 to 28 days in knowing that chronic illness has several places you be readmitted and then there's lack of funding for that without the reimbursement so both of these present significant barriers to access and I think that it could offer a way for us to look at across a few states.

Susan Tanksley:
Thank you for bringing that up and including that in the discussion. I will also suggest to be sure to talk there are other activities that are looking exactly at those issues that are being conducted within the regional genetic collaborative with support from the national coordinating center and actually sickle cell is one of the examples they are looking at with the benefits that may not be covered under the Affordable Care Act. Some of that is going on so I would be very hopeful to interface with those groups and those activities.

Joseph Bocchini:
Joan, is that being done in an organized fashion amongst all the collaboratives or specific some collaborative are looking at certain issues related to that?

Joan Scott:
It is a coordinated effort to some of the regional collaborative do have their of their own projects but there are -- there is a coordinated and Jill can explain it better maybe [Indiscernible] who are here, but there is a joint project that is being conducted in using two conditions as examples, sickle cell and PKU is the other example.

Joseph Bocchini:
That certainly can be --

Unidentified female:
We are very interested in that. Bob Ostrander and a number of us, Andrea [Indiscernible] a number of us have been very interested in taking this opportunity when this changes in how healthcare is delivered to make sure to the extent that we can find out if there are any unanticipated adverse consequences we identify them and take the opportunity before it passes us by to make sure things are good.

Joseph Bocchini:
Cathy?

Cathy Wicklund:
Carol, do you think that you can describing the process or [Indiscernible] is one aspect and you might uncover access issues and doing so versus a more targeted exercise to identify access issues. So do you feel like with that particular question that you will get at all the access issues or do you feel like it is almost like a byproduct of looking at this particular issue?

I'm trying to think about the scope of information that you're going to get.

Carol Greene:
I think in the process of developing a specific project it will need to be made even more clear and I think that the two things that we are interested in that are not mutually exclusive that really come out of this of the work before is that we are interested in access and we are interested in making sure that there is data to be able to judge do people have access, are they getting good care. I think it is possible to do both of those. I think the language is a little broad, public health clinical interface, that could lead you to look at how does Medicaid relate to private payers but we are really focused in on the after newborn screening and long-term care for a job so I think that in and of itself will narrow our focus because we are not -- we are a long-term follow-up of a HRSA committee and I don't think we are looking at all of public health meaning all of healthcare but really focusing there. I don't know if that's a good answer but clearly we will be working with [Indiscernible] Chris and Charlie will be working with Debi and Joan and Joe and make sure that it is described in the way that defines a doable project. So I think your question is really important and I think the focus that most of us are interested in is the combination of is really the focus is on access and better outcomes and in order to do that you also have to look at data. Existence of data.

Joseph Bocchini:
Other questions or comments? I think the consensus is that this is a good topic and that we would like the subcommittee to pursue it and then as you say we are really way up here appear now and so in the next couple of months as you meet you can begin to flush out specifics and how it down to -- September meeting you will come back with a little better idea of how --

Carol Greene:
I should say very group -- it looks like Charlie and Chris and I are working together we had really hoped that we would at least have something in a broad sense and then our goal between now and the next meeting is to finish up the edits of the Priority C paper and to use those monthly conference calls to come up with more specifics that I personally think we can come up with a really good project that will clearly address what Andrea brought up, what I care about, Charlie and Chris and the whole group and that we will use that time to come back with more specific plan.

Joseph Bocchini:
Thank you for your report. Thank you for your work and we will now move to the next presentation but before we do [Indiscernible] representative [Indiscernible] [Indiscernible--Muffled audio]. I would like to identify those people who are here for this session. [Indiscernible] [Indiscernible--Low volume] So Freddie?

Freddie Chen:
(Low volume)

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Joseph Bocchini:
The record was so state that. That training. -- Beth Tarini is here. Susan Tanksley, are you on the phone?

Susan Tanksley:
Yes, I am.

Joseph Bocchini:
Great. And then Adam Kanis, are you on the phone?

Adam Kanis:
Yes, I am.

Joseph Bocchini:
Okay. Thank you. Natasha Bonhomme are you on the phone?

Natasha Bonhomme:
Yes, I'm here.

Joseph Bocchini:
[Indiscernible]. Carol Greene is here. Thank you all very much. Next we will go to the education and training subcommittee report that Beth Tarini will provide us with that report so Beth?

Beth Tarini:
Thank you and it is never good to stand between everyone and leaving. I heard some important people have [Indiscernible] I'm going to go quickly and leave the time for discussion. So the first slide as you'll see I'm co-chair, Don Bailey is the chair. He's the outgoing chair. I'm filling in for him today. The chair elect is our very own Catherine Wicklund. She will be assuming the duties – duties in September as chair. Thank you. Our agenda the agenda we had with introductions -- from committee members which I will skip in interest of time. We have went over a final summary and next apps regarding our priorities. Next slide.

Priority A for those of you may not remember was to track, provide input on a facility integration of national education training initiatives. Next slide.

So the review as with actual project we did under that priority is to identify conditions not part of the RUSP and for which screen entry meant will mostly almost like a granular l it a pick we chose those conditions to represent a variety of clinical characteristics such as it up is this, age of diagnosis, clinical morbidity and then in partnership with the professional and current organizations, identify major education and training needs for each condition.

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We addressed the six conditions to guide our assessment. Today this meeting what we did were to summarize the major issues and themes that emerged from this work across these three paradigm conditions. I'm going to show you the overall themes, not the actual specific data. Next slide.

So for each question, we found for the typical pattern of identification of children with these conditions, so that the conditions shared to some degree that the two of them were identified after clinical symptom developed over federal extent that was development will delay, usually a presenting -- John is a virtual system and then I wasn't even adults. For long QT you have a paradigm where the dedication pattern is consistent as a dental findings unaffected family members which trigger an evaluation or in some small cases not necessarily always in this country population-based screening. Next slide.

And what problems exist with the current pattern in each of those are for fragile X not all children at risk are tested. For long QT you can die before you're actually identified and for Wilson's disease their variable and not specific symptom presentations which complicate the ability to identify the affected individuals.
You see the space there is because there's what other problems with actual identification and what are the implications so the indications and fragile X if you're not an invite the children at risk the missing an opportunity for evaluation and early intervention. Also brings up the other issue which is comes up another disorders is future potential to maybe born before the index child is identified. And wanted to you have the issue of identifying someone with this disorder but having a challenges to predicting the clinical severity of that disorder and in Wilson's disease you may have clinical progression and morbidity such as liver damage before you can identify do the individual. Next slide.

Would population screening outside the newborn period be at all feasible or desirable? Yes, [Indiscernible] a major task of ours is to assess screening so the challenges as they exist and not surprisingly education of clinicians, the determination of clinical severity and genetic testing. We can also add education of the public to all of these as well. Next slide.

In the absence of population screening the best case scenario or identification is to increase the awareness and education for all of these about the clinical the risk factors or clinical symptoms that should trigger an evaluation. We came also with fragile X discussion about the possibility of panel testing after densification of clinical symptoms in some children with the volatile the late – including fragile X testing on the panel might be useful. Next slide.

We identified the efforts needed in each of these paradigms I'm (Inaudible) substantial involving education, access, testing development and prognostic determination. Next slide.

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The stakeholders and all across all paradigms not surprising, premier care providers come to specialist, public health (indiscernible) patients and their families. Next slide.

The points in this priority can I want to reiterate, was not to say and I will say the priority that was voted upon by the committee, the point of the priority was not to say that one of these disorders should be added to a RUSP but we should endorse population based screening, the point of the priority was to use these as per times to begin the discussion about should you come forth at any future time about population screening outside of the newborn period.

Priority B, that was completed and that was to promote newborn screening awareness among the public and professionals. At the other meetings we had worked with APHL and CDC for the anniversary celebration.

Priority C, that is to provide better guidance for advocacy groups and others regarding nomination and review process. Next slide.

This priority has had that some past efforts which I will summarize. Which have involved the [Indiscernible] vision of [Indiscernible] website to help it become more user-friendly. To the lay public. As well as the public summary document of the SACHDNC process in that case we've done drafts commission views of advocates to identify important issues have been done, graphs of those have been incorporated and that remains in continued development. Next slide.

But what we have been in done in trying to get something accomplished on this priority is Jeremy Penn one of our members has helped us develop, is helping us with the development of a glossary of terms to be incorporated into the SACHDNC website, potentially. If we cannot change the website or a heroic effort to make massive tinges on a website, if it is a heroic effort to create documents extent of documents -- Meeting a long time this public and they just perhaps at the very least we can CHIP away at it by having be able to better define the terms that the parents or public or advocates may see on the website and so we have started the glossary of terms. We reviewed it yesterday and will continue to review and we will have feedback from committee members on the readability and then next slide --

Next steps are to revise the glossary to an appropriate reading level be delivered to work on the implication logistics with our not that means -- that means identify the program location for the website actually should say for the classroom whether that is on the SACHDNC website, on a clearinghouse [Indiscernible] alliance to find a place with these glossary terms which would apply specifically to the picture process could be housed. Next slide.

So the next steps for the committee, the subcommittee I should say are that our priority objectives have been completed. We will finish up the glossary in the interim and in my opinion and those others may jump in we will move forward identifying go forward

identify future priorities are weak to hear from the committee as to priorities they have that they would like us to evaluate. [Indiscernible].

Joseph Bocchini:
Thank you, Beth. Questions or comments?

Unidentified female:
Thanks, Beth, appreciate that update. I'm a little unclear about what you were doing with number one. Priority A? What's the next steps there?

Beth Tarini:
This was a final step. This is the summary.

Unidentified female:
That was the final step? Was the product?

Beth Tarini:
This is the product. This -- these slides on the product. We were not told we required a white paper. Unless we misunderstood.

Joseph Bocchini:
I think we wanted to make sure we identified what barriers might exist -- that might be different for a later onset or a later review I think that was one of the key issues that we really wanted to address and barriers for all stakeholders including public health related to doing this and I think in previous presentations [Indiscernible] did have some data or some things related to -- addressed feasibility.

Beth Tarini:
My data comes from Don's. So I don't – he may have framed it and that way and I'm happy to reframe it as a barrier, I think these issues can be reframed as barriers, if you wish. In a short a summary to be submitted to the committee. But if that would be helpful. I'm not sure a white paper is what you are looking for or a simple summary. Okay.

Joseph Bocchini:
Let's consider that further perform we make a decision on that. So let's suspend that for the moment and see if there are additional questions or comments. Dieter?

Dieter Matern:
Given what we heard earlier from Mike Watson, do you need a stakeholder from the payers at the table? Maybe a representative from CMS to clarify why they think this is not important?

Beth Tarini:

I'm not sure – not important. We would ask them what are the current barriers I suppose. We are happy to invite CMS to be evaluated. I guess the question I would have for the committee is how deep would they a like us to go into this process? We are fine to go down the issues of cost. Spin

Unidentified female:
I guess the question is I think we were talking about yesterday was it wasn't necessarily an exercise, I don't think it away that we would choose one of these that would be tragic and went or make a decision that would be -- I don't know -- it would be premature to talk to CMS about something like this given all the other issues that we have. I guess -- [Indiscernible] main barriers that you need to this is really about the or was it [Indiscernible--Low volume] right now with newborn screening we are comfortable with the mandatory aspect of that come up but to have something in place that Jeff like at a one year old whether that would be mandatory I think that's a very unique issue about this particular exercise.

Jeff Botkin:
Not specifically on the question but I think one of the things we did with this exercise was didn't really map it directly to the criteria or the framework and that might've been an alternative way to think about these issues but we didn't really explore as I recall in detail was the sensitivity and specificity of each of the test for these conditions and how would they -- would that support a population-based screening or not. Then board -- go into great detail about what would care providers look like for identified -- we didn't dig too deeply into each of those criteria that might actually be quite important in thinking about a decision.

Beth Tarini:
For two reasons I think one it was intentional to separate so that people did not confuse this exercise with assuming we were giving a leg up or implied we are giving a leg up to one condition to be a future candidate for their RUSP – very sensitive in that regard. That's why we did not address this might use those guiding principles of the Dr. Kus. Second, I was the frankly, the scope of such a project be beyond that of the subcommittee. To have -- those are quite frankly comprehensive reviews that large grants are funded for. So I think that the point of this is this was meant to be an overall guiding review and you have 30,000-foot view over what are those issues that would be addressed first line in a child newborn screening program.

Unidentified female:
Where'd you go from here?

Joseph Bocchini:
That I will turn back to the committee. I think --
To me I think the major goal was to determine and [Indiscernible] selected to look at the different parameters that might be needed to make a diagnosis. But what overall would we face if we were going to address genetic disorder for which screening would be

recommended [Indiscernible] [Indiscernible--Muffled audio] so that was the primary thing was to see whether the [Indiscernible] because we were talking about initially that this committee is responsibility for newborn and children and obviously newborns the system was in place and it was going to be in proved and so that's where the money was in the beginning so now we are thinking what happens if we go to older age group and what would potentially be the barriers to the 3 that were selected by the group to consider but like you said, at a very high level overview not that we would be promoting screening for these but what were the issues that might arise relative to that. I think that getting a better idea of the barriers that we might pays for each of those stakeholder groups and like you said, one of them would certainly be mandate versus the fact or how that might be addressed or if it makes it not feasible to consider. That's sort of the overall goal. In a summary that could end up as some form of a presentation or publication that would address some of the potential barriers to screening at a certain age group, public health --

Beth Tarini:
We can certainly ago -- we can certainly collect opinions from these different stakeholders and reviewed the literature to see what have been identified and added to the summary.

Joseph Bocchini:
So is it the sense of the committee to go forward with something like that?

And then we will go -- any comments from the committee on this point?

Cathy Wicklund:
So are you suggesting that with the stakeholders that we've identified and perhaps might need to expand on that we contact those individuals. -- qualitative --

Joseph Bocchini:
Yes. But on the subcommittee we should have enough representation from the different groups to be able to give you a general idea of what might be some of the issues that could potentially barriers? Or should we go there or is it is a possibility for the committee to go there or are we limited based on this not being a feasible approach?

Joseph Bocchini:
[Indiscernible] you had a comment?

(Indiscernible name) Unidentified female:
Just wanted to ask about the possibility of (Indiscernible) looked for in children but also how to integrate the [Indiscernible] testing [Indiscernible] care of the child because as an obstetrician [Indiscernible] we are doing tons of prenatal screenings and the barrier I see is that is going into pediatric is our press and all the testing has to be read that and it could be [Indiscernible] all these things [Indiscernible] know what happens to the [Indiscernible] I guess I'm making the suggestion to think the [Indiscernible] child health

and I don't really want to throw another barrier in but how can connect as a value-added [Indiscernible] [Indiscernible--Muffled audio] we heard about the [Indiscernible] is what more data happening -- how can we connect it.

Beth Tarini:
I feel like you were there. We had that explicit discussion and especially with fragile X about why would you in some cases fixate on , childhood screening if so many are coming into the pipeline with screening prenatally. The decision or discussion that led to that potentially was beyond the scope of the committee but it was discussed as a barrier quite frankly also because if one of your screen is -- or a lot some degree is getting picked up prenatally it creates -- it is an issue. Did Joan have a question?

Unidentified female:
Thank you.

Joan Scott:
What we are talking about here is moving something into a public health realm. The CDC publishes what they have tier one, tier two, tier three genomic test about what the tests they think our ready to move into a public health realm as opposed to maintaining just in the clinical setting and what I could not remember is if there was any tests, any genomic applications in their Tier 1 which they felt was ready for public health that was a pediatric in nature and that's why --

[Overlapping/Multiple speakers]:
To see whether or not there was

Beth Tarini:
No doubt most of these are in the clinical setting.

[Overlapping/Multiple speakers]

Unidentified female:
They rely upon clicker presentation as the first trigger to evaluation.

As opposed to what this committee looks at [Indiscernible] within the public health realm. So it might be worth it just to peruse Tier 1 newborn screening is there. That's good to know. As to whether or not any of these other -- the only reason I bring it up is I know that are -- there are other groups that have looked at this issue of when do we start thinking about things from the public health perspective as opposed to remaining in the totally in the clinical area. And the challenge of moving things into the public health realm.

Joseph Bocchini:
That's additional feedback for the subcommittee. Hearing none, I think the last item on the agenda was to see if there was any further discussion about other topics to come to

this before the committee. I think we've already identified a few that would be beneficial. Any other final comments then?

Unidentified female:
I had one comment. I'm wondering if there's any opportunity to disseminate some of the public health impact work that the committee is doing more broadly to the public because it seems like that's one of the issues that's important for us to explain why it is affecting a lot of the decision-making around and [Indiscernible].

Joseph Bocchini:
That's a good point. Number one, I think that we will put together a publication that will then be put on the committee's website and I think that we can certainly consider other ways to disseminate this information once it becomes finalized. Spend [Indiscernible--Muffled audio]

Unidentified female:
And maybe a Cliff note version. (Indiscernible)

Joseph Bocchini:
Okay, thanks.

Any additional comments? I think there's one other item that there's been some discussion about seeing if we can develop relationship with a specific journal that would publish all of our committee report so that we would have an ongoing relationship with a journal. Is that something that the committee would be and rested in pursuing? -- be interested in pursuing? Think about that and then if there is some interest stomach wasn't there one with another [Indiscernible] but the committee has done has been

Unidentified female:
[Indiscernible--Muffled audio]

Joseph Bocchini:
Right. I think that's been where they have been submitted but this would be making a relationship with the formal funding relationship. Yes?

Iris Mabry-Hernandez:
Just as experience with the U.S. Preventative Services Taskforce has a relationship with a journal so it is a very positive thing so recommendations that about would be published and handled if it is dealing with topics in pediatrics so it is nice to have an established relationship where it you can have -- you still have to go through peer review but they have an established a channel to have a place for your product.

Beth Tarini:
I was going to add we started that at the IOM Roundtable. We have Greg [Indiscernible] is the genetics editor for (Indiscernible) and it is been a nice -- we've kind of in a

workshop reports are out we have a white paper or a commentary that goes along and it is also a much more doable because the commentaries out because their about Page, page and a half which is a lot more doable than really try to put in a long report and you really draws attention into the actual product itself so they can also how we can do this in a way that is doable.

Joseph Bocchini:
Okay, additional thoughts?

Joan Scott:
I was just going to suggest if you go down that path this is more of a lead process but if you have cap publication of being able to have a published also having the copyrights [Indiscernible] sometimes there's that issue so have that type of understanding that publisher but is also going to be simultaneously posted on our website if you choose to do it that way.

Joseph Bocchini:
That's a good point. If you would ease each consider what potential Journalist that we might be the with think that we should consider, please let us know and then we can go forward with that concept. All right. Jeff?

Jeff Botkin:
The idea of a potential agenda item something that's, your degree over the years is the question of whether the committee be looking at conditions of that ought to come off the RUSP and what would the process look like to evaluate that's what a possibility. I don't have any candidates in mind but if others do, should we'd be thinking about that as part of our portfolio and what would that process look like?

Joseph Bocchini:
Okay, thank you. That's a good topics to consider. Dieter?

Dieter Matern:
I thought that the process is pretty much the same as the recommendation to include a condition? I think it there regional [Indiscernible] was already in the algorithm outline how you can [Indiscernible] add and remove conditions from secondary to primary targets so I would suggest there's a condition that people feel strongly about their bring it to the committee and ask for removal and then it would go through some kind of evidence review.

Joseph Bocchini:
Okay. We could consider a more broad discussion of that at a later meeting. Other items? Alright. Hearing none I want to thank everybody for their participation in this meeting. I think that a number of things were accomplished and appreciate everybody's input. Both here and on the telephone. And all the work that was done between

committee meetings to bring these topics forward in a good way. So again, thank you all very much. I appreciate your involvement. That will conclude this meeting. Thank you.

That concludes today's conference. All participants who dialed in by phone may disconnect at this time.

[Event concluded]