ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN
Transcript of Web Meeting - Tuesday, May 12, 2009 - 1:00 p.m. - 5:00 p.m.

HRSA Genetics Web Meeting

>> Rodney Howell:

This is Rod Howell, and let me welcome everyone to the 18th meeting of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. [Inaudible] that we have a new Secretary of Health and Human Services: Kathleen Sebelius was sworn in as the 21st Secretary of the Department of Health and Human Services on Tuesday, April the 29th. As governor, Secretary Sebelius expanded Kansas's newborn screening programs, put a new – renewed emphasis on childhood immunization, and increased the eligibility for children's health coverage. So we welcome Secretary Sebelius and look forward to working with her as we proceed.

Before we actually begin the meeting, we need to have Dr. Puryear take an official roll call. Michele?

>> Michele Lloyd-Puryear:

Dr. Alexander? Dr. Boyle?

>> Coleen Boyle:

Here.

>> Michele Lloyd-Puryear:

Dr. Buckley? Dr. Calonge? Dr. Dougherty – I know she's going to be late. Dr. Frempong?

>> Kwaku Ohene-Frempong:

Yeah, with bad laryngitis.

>> Michele Lloyd-Puryear:

And Dr. Kelm? I know you signed in.

>> Kellie Kelm:

Here.

>> Kwaku Ohene-Frempong:

Here.

>> Michele Lloyd-Puryear:

Ms. Monaco? I know you signed in.

>> Monaco:

Here.

>> Michele Lloyd-Puryear:

Okay. Dr. Rinaldo?

>> Rinaldo:

Here.

>> Michele Lloyd-Puryear:

Dr. Skeels?

>> Michael Skeels:

Here.

>> Michele Lloyd-Puryear:

Dr. Trotter?

>> Tracy Trotter:

Here.

>> Michele Lloyd-Puryear:

Dr. van Dyck?

>> Peter van Dyck:

Here.

>> Michele Lloyd-Puryear:

Dr. Vockley?

>> Vockley:

Here.

>> Michele Lloyd-Puryear:

We have a quorum.

>> Rodney Howell

Did anyone else appear since we started the roll call?

>> Duane Alexander:

This is Duane Alexander. I just joined.

>> Michele Lloyd-Puryear:

Thank you, Duane.

>> Rodney Howell

Thank you, Duane. I'm going to also ask Ms. Harris to go over a few logistics for the call before we proceed. Alaina?

>> Alaina Harris:

Thank you, Dr. Howell. I want to remind the committee members and the organizational representatives and speakers that you are on an open phone line. That means we can hear you when you talk. The members of the general public are on a listen-only line. So to eliminate background noise, we ask that you keep your phones muted when you are not speaking. If you do not have a mute button on your phone, you may press star-6 to mute or unmute. And we ask that you be advised that when you use the star-6 function, that will not work if your phone is in speaker phone mode, so please keep that in mind. And also, every time you press star-6, it makes a beep on the line, so we can hear you when you mute yourself. Also, if you have to leave your desk to take another call, or for whatever other reason you might need to leave your desk, we ask that you do not put your phone on hold, as your hold music will then come on, and that will play during the conference call. We do ask that you speak clearly and loudly so that everyone can hear and understand you. Also want to remind you that today's call is being transcribed, so please identify yourself before speaking, as the transcriptionist and the note taker will need to accurately record your comment. So if anyone speaks without identifying themselves, the transcriptionist has been instructed to ask the caller to state his or her name for the record.

>> Rodney Howell

Thank you, Alaina. Now we also need to ask Michele – if she would also go through the attendance list for the official representatives to the advisory committee.

>> Michele Lloyd-Puryear:

And I first want to confirm – Dr. Buckley, are you online? Did she sign in? Okay.

>> Rodney Howell:

Dr. Buckley's signed in, and we expect she will appear soon.

>> Michele Lloyd-Puryear:

Dr. Calonge? Okay, and did you sign in yet? Okay. So, Dr. Getchell? [Pause] I know you've signed in. Dr. Burton?

>> Barbara Burton:

Here.

>> Michele Lloyd-Puryear:

Dr. Chen?

>> Frederick Chen:

Hello, I'm here.

>> Michele Lloyd-Puryear:

Okay, thank you. Dr. Geleske? Oh, he's not on, okay. Dr. Kus?

>> Christopher Kus:

Here.

>> Michele Lloyd-Puryear:

Dr. Musci?

>> Thomas Musci:

Here.

>> Michele Lloyd-Puryear:

Is Ms. Terry here?

>> Sharon Terry:

Here.

>> Michele Lloyd-Puryear:

Dr. Watson?

>> Watson:

Here.

>> Michele Lloyd-Puryear:

And Dr. Willis?

>> Mary Willis:

Here.

>> Rodney Howell:

Excellent. I would also like to welcome a new organizational representative from the Department of Defense, Dr. Mary J.H. Willis. Dr. Willis graduated from the University of San Diego with a bachelor's degree and earned her Ph.D. in biochemistry from the University of Colorado. She went on to earn her M.D. also from the University of Colorado in Denver. She completed her pediatrics training at the University of California-San Francisco – San Diego; excuse me – a little further south. And is board certified in clinical genetics and pediatrics. Dr. Willis is a fellow of the American Academy of Pediatrics and a member of the American College of Medical Genetics and a member of a number of professional societies. Dr. Willis serves on the Department of Defense Newborn Screening and Integrative Process Team. And Dr. Willis, we welcome you greatly to this committee to represent the Department of Defense.

>> Mary Willis:

Thank you.

>> Rodney Howell:

At our February meeting, we announced that Dr. Piero Rinaldo was there for his last meeting. Actually, we gave him a certificate as a committee member. However, Dr. Rinaldo will stay on as a committee member. And so, Piero, we welcome your continued efforts, in spite of the fact that you have a certificate.

As a reminder, and a very important reminder, the Committee is accepting nominations for two positions for individuals with expertise in bioethics and infectious diseases. The nominations and supporting materials are due Monday, May 18. Information about the application process is available on the committee Web site, and I think you have that, but it's www.hrsa.gov/heritabledisorderscommittee. The following information must be included in the package submitted to each individual nominated for these positions. One is a letter of nomination, the nominator's contact information, and a current copy of the nominee's curriculum vitae. Let's now look at the minutes from the February meeting – the minutes, which is under Tab 5 in the members' book. And are there corrections to the minutes of that meeting? Are there any objections to the meeting? [Pause] We need to have – I guess we'll have to do a voice vote, Michele; is that right? So can we go down the list?

>> Michele Lloyd-Puryear:

We need somebody –

>> Rodney Howell:

We need someone to make a recommendation that the minutes be approved.

>> Tracy Trotter:

This is Tracy Trotter. So moved.

>> Rodney Howell:

And is there a second?

>> Gerard Vockley:

Jerry Vockley seconds.

>> Rodney Howell:

Thank you very much. Now Michele will have to go down the list to keep a record of who said yes and no.

>> Michele Lloyd-Puryear:

Dr. Alexander?

>> Duane Alexander:

Yes.

>> Michele Lloyd-Puryear:

Dr. Boyle?

>> Coleen Boyle:

Yes.

>> Michele Lloyd-Puryear:

Dr. Buckley? So… Dr. Calonge? Dr. Dougherty's not on. Dr. Frempong?

>> Kwaku Ohene-Frempong:

Yes.

>> Michele Lloyd-Puryear:

Dr. Kelm?

>> Kellie Kelm:

Yes.

>> Michele Lloyd-Puryear:

Ms. Monaco?

>> Jana Monaco:

Yes.

>> Michele Lloyd-Puryear:

Dr. Rinaldo?

>> Piero Rinaldo:

Yes.

>> Michele Lloyd-Puryear:

Dr. Skeels?

>> Michael Skeels:

Yes.

>> Michele Lloyd-Puryear:

Dr. Trotter?

>> Tracy Trotter:

Yes.

>> Michele Lloyd-Puryear:

Dr. van Dyck?

>> Peter van Dyck:

Yes.

>> Michele Lloyd-Puryear:

Gerard Vockley?

Gerard Vockley:

Yes.

>> Michele Lloyd-Puryear:

Dr. Howell, do you [inaudible]?

>> Rodney Howell:

Yes.

>> Michele Lloyd-Puryear:

So it's unanimous.

>> Rodney Howell:

Thank you very much. Let me point out several items that are in the committee booklet or that were sent to you as a PDF file under "Committee Correspondence." One is that we have received a new nomination – a new condition of nomination, and that's a condition that we have not yet had a preliminary review that we'll have to do before it comes to the committee. It is on thalassemia. And that is Dr. Elliott Vichinsky from the Children's Hospital in Oakland. Under "Correspondence," you will also find two letters to the secretary. One is the medical foods letter that was approved by this committee and sent in March of 2009. And there's also a copy of the letter that the committee sent to Dr. Jennifer Puck, who is a nominator of severe combined

immune deficiency. We also have an e-mail from Dr. Edward Bartlett to follow up on comments he made during his presentation at the February meeting concerning the translational research policy session. He has sent the Federal Register notice from the Office of Human Research Protections, which is requesting information and comments from the public about whether or not the office should pursue proposed rulemaking to enable the Office of Human Research Protections to poll IRB and the institutions and organizations operating IRBs directly accountable for meeting certain regulatory or requirements under 45 CFR part 46. You have until June 3 to submit any written comments to Dr. Bartlett, and the committee has this material. There are a variety of other items that are noted, an interesting one of which is – PerkinElmer had sent a notice about their contract to supply newborn screening cards. And of course, others also continue to supply cards also.

Let's move now to our major item of business, which is an update on the nomination for severe combined immune deficiency. You will note in your briefing materials under "Correspondence" that we've included a copy, as I just mentioned, of the letter that we sent to the nominator for SCID. You will see that we've outlined five areas where there were gaps in evidence. And those five areas were, one, a perspective identification of at least one confirmed case of SCID through a population-based newborn screening program; demonstrated willingness and capacity of additional States to implement newborn screening for SCID; reproducibility of the screening test and continuance of false positive rates of under .1 percent; absence of the laboratory proficiency testing, although it's anticipated that quality control materials will be made available by the Centers for Disease Control and Prevention (CDC) by June; and number five was an accounting of cost accrued in implementing newborn screening for SCID and availability of resources to appropriately address the cost.

In the letter that was sent to the SCID nominator, Dr. Puck, you will note that we will reconsider our nomination after new evidence is available on those subjects. Now, we have – there's been a goodly bit of discussion about SCID and the nomination and so forth, and we have two persons that we've asked to make a presentation, as you will see in your agenda. The first person, Dr. Bob Vogt from the newborn screening branch of the Division of Laboratory Sciences at the CDC – I think many or most of you know Bob. He trained in immunology, toxicology, and experimental pathology at Hopkins and has been at the CDC for over 25 – or approximately 25 years. He also serves as primary – principal investigator for the Newborn Screening Translation Research Initiative, a cooperative effort with the CDC foundation and public health academic and corporate partners. And Bob, I would like to have you discuss what you are proposing for pilots and also some comments about the proficiency testing samples, if you would please.

>> Robert Vogt:

Thank you, Dr. Howell; I'd be glad to do that. So I think most of you all know that CDC issued a funding opportunity announcement last year for two awards to begin pilot programs for newborn screening for SCID, and awards were made to Wisconsin and to Massachusetts. And again, I think you all know from the February meeting that both of those programs are going now. They're on the street, so to speak, and essentially every baby born in Massachusetts and every baby born in Wisconsin is currently being screened for SCID and other immune deficiencies which would result in a strong decrease – a severe decrease in the recent thymic immigrant T

cells –the so-called TREC assay. The assay is based on detecting the small piece of DNA that is excised from lymphocytes uniquely when they become T cells. And that assay had been developed originally for newborn screening by Jennifer Puck. It had also been developed independently at CDC in the HIV-related laboratory program by Chin-Yih Ou. Both assays focused on using bloodspots as the sample matrix. And we'd adapted Chin-Yih Ou's assay, and Jennifer published hers in 2005. Massachusetts and Wisconsin are running that assay. They are, in principle, the same assay; there are some differences with respect to the exact reagents.

And we conducted the first inter-laboratory evaluation of candidate materials for proficiency testing and QC about 8 weeks ago. We sent out materials that consisted of leuko-depleted cord blood admixed back to the original cord blood, so there were degraded degrees of leukocyte depletion ranging from 100 percent of original leukocytes down to fully depleted and five different concentrations in between. Those materials were sent out in both an identified fashion and also some materials in a blinded fashion. And they were sent to the Massachusetts laboratory, the Wisconsin laboratory, the California – Jennifer Puck's laboratory, and analyzed in our own laboratory. We have those full sets of results, and in every case, all laboratories found an expected dose response gradient. The exact values for the readout, which in real-time PCR is a parameter called the cycle threshold, were close, not identical. The slopes were also close, not identical. But in general, the assays appeared to be comparable between the four different laboratories, and the materials seemed to perform well.

Now, the next refinement we want to establish is to make a material that looks more like a T cell immune deficiency. So instead of depleting all leukocytes, we would deplete T cells only. And those materials are being pilot-prepped and evaluated in our laboratory. We've also established a partnership through Jennifer Puck with an organization in California called the Immune Tolerance Institute, which is linked with the Immune Tolerance Network, which is supported by NIH. But the Immune Tolerance Institute is not supported by NIH. So their chief science officer, Aaron Kantor, and I have been corresponding, and they will be making materials, and we will cross-evaluate those materials. And we think this will be useful in having two different sources and being able to compare results between those sources. We are also working on a reference method that would employ a platform that is not generally available for newborn screening laboratories, but which we think, and Jennifer and the folks at the Immune Tolerance Institute think, would provide the best accuracy base for reading out the number of TREC-bearing cells in a bloodspot. And that assay is in development at our laboratory. It is in development through Jennifer at the company that makes the platform. And the intent is to port that over to the Immune Tolerance Institute. They have purchased that instrument for that purpose.

And I think, Dr. Howell, that is pretty much the story to this point. We will have another send out later this month, and we are aiming for it to be the T cell-depleted material. We're still evaluating pilot preps in our own laboratory for that, so I cannot tell you that we have that ready to go yet. But things right now look good, and I think we are on schedule for having materials available. And we are required by virtue of the cooperative agreements with Wisconsin and Massachusetts to provide such materials as our part of those projects for those two States. And clearly, any materials that we make available for that purpose would be available for any program that wants to engage in pilots and ultimately apply the public health screening for T cell immune deficiencies.

>> Rodney Howell:

What is the deadline– what's the time frame of having those materials available for the two States and other States?

>> Robert Vogt:

I think, Dr. Howell, what we talked about earlier is right some time in late June through mid-July. We want to get at least two round-robins among the four laboratories with prototype materials. But we're making enough of them so that as soon as we have that information, we would have materials on hand.

>> Rodney Howell:

Now, do you have plans – immediate plans for added additional pilot States at this point?

>> Robert Vogt:

We don't have funding for that, Dr. Howell, so we are eagerly awaiting the availability of funds through the Translational Research Network or what other funds might be available through NIH, and we certainly have been in communication. We understand that there is a desire to look at larger populations. And we have made the folks in the larger States aware of the fact that we would provide all the technical support we're capable of, should they wish to engage in a pilot program.

>> Rodney Howell:

Now, are you looking at any other diagnostic technologies other than TRECs that might be useful for the immune deficiency newborn screening?

>> Robert Vogt:

We are, Dr. Howell. It's an excellent question. We are working with Ken Pass; we are actually officially part of the NIH New Technologies Contract that was awarded to Dr. Pass and the Wadsworth Center. And one part of that, which I believe was actually supplemented after the original contact was awarded, was to look at an alternative assay that would measure another T cell-specific marker, in this case, a surface protein called CD3, and a response marker – a biological response marker, interleukin 7. There have been reports that those two assays can be used to detect T cell deficiencies, although there have also been unpublished reports that that doesn't work as well as the published reports suggest. Dr. Pass's laboratory is making terrific progress on those assays, and the same materials that we're preparing for the TREC evaluation calibration quality control would be suitable for the CD3 component of the assay. And we are working with Dr. Pass to spike those materials with interleukin 7. The idea behind those assays is, you would see a depletion or failure to detect the T cell-specific protein, CD3. And at the same time, he would see an elevation in the T cell growth factor, interleukin 7, because of the immune system's attempt to correct the defect. So it's a yin-yang sort of thing, which has a nice,

attractive feature for screening, not unlike the T4-TSH combination for detecting congenital hypothyroidism. And that will require additional development of materials, because biologically, we can deplete T cells, but we will need to add the IL7 in as a separate component. That will not interfere with the TREC assay, so our intent is to make materials that were suitable for any assay that is based on measuring T cell markers and the T cell growth factor, interleukin 7.

>> Rodney Howell:

Are there plans to simultaneously do Ken's assays on samples that are also simultaneously studies for TREC numbers?

>> Robert Vogt:

I think, Dr. Howell, that is absolutely critical and will require large numbers of symbols to look at the – what I'll call the hit rate and – as well as reference samples of newborn spots from children who were known to have SCID. Now, the reference spots are available through the arrangements that Dr. Pass has made with Statens Serum Institut in Denmark, and Dr. Norgaard Pedersen has actually found those spots and pulled them and has them in frozen storage. But those are extremely precious materials, and because those assays are biochemical assays and not DNA assays, if you make that kind of distinction, the question of assay stability – analyte stability is paramount. So we know with the interleukins that there is a stability issue, and with the membrane protein CD3 stability has not been evaluated. So Dr. Norgaard Pedersen will be pulling control samples of comparable aged spots from normal infants, and those very precious samples will not be analyzed until Dr. Pass is quite confident in the performance characteristics of the multiplexed assay to measure the two markers.

At that point, we would be prepared to look for a way to evaluate a large population of newborn dried bloodspots by both methods, and that will be an essential component. At this time, however, we have not identified a funding source for that project.

>> Rodney Howell:

Thank you very much. I think it's also important to point out that it brings up once again the absolute vital nature of having appropriately stored dried bloodspots for study. And again, we all know that Dr. Norgaard Pedersen has detailed published material on the informed consent and other subs– other materials that substantiate his ability to use these dried spots in an ethical and secure way and so forth. Any further comments or questions on this –

>> Rebecca Buckley:

Yeah, this is Rebecca Buckley. I have a couple of questions of Dr. Vogt. The spots from Denmark – are they going to be control and SCID babies, or – do you know?

>> Robert Vogt:

Well, yes, absolutely, Dr. Buckley. They will provide both control and age-matched, gender-matched – when I say "age," I mean age of the dried bloodspot match – materials to Dr. Pass.

>> Rebecca Buckley:

Okay. The second question is, the instrument that you were talking about, the new platform for reading these out – is this an expensive instrument, or do you know what it is?

>> Robert Vogt:

Yes, it is expensive. We purchased it last year - the Sequenom mass array system, which is a mass spectrometry readout for measuring nucleotide sequences. It has all of the quantitative accuracy and specificity of the mass spectrometry. And they have a quantifying method called competitive PCR, which is different than real-time PCR. In fact, I found out competitive PCR is a precedent technique that was used with reading out bands on gels many years ago.

>> Rebecca Buckley:

Right, it was the first one, right.

>> Robert Vogt:

It was the first one. And when I went around telling everyone how this was a new technique, I got told how wrong I was. But the readout on the mass spectrometer is a step upward, I hope, because it sure costs enough. So we have that platform, and the Immune Tolerance Institute has the platform. We have gone through two training sessions; the platform's working in our laboratory. There is some issue with respect to assay development. There is not a working assay for TREC competitive PCR in Sequenom at this point. So that is an assay development situation, and I cannot protect at this time how quickly or smoothly that will go. My understanding from Jennifer is that the folks at Sequenom are working on it.

>> Rebecca Buckley:

I guess the goal of that was to try to standardize the readout from lab to lab; is that correct?

>> Robert Vogt:

That's exactly right, and with an independent platform so that there would not be discussions about platform dependency. We do not expect Sequenom to appear in every newborn screening lab any time soon. It's about a half a million-dollar system installed and running. The cost of running it is substantially less compared to using fluorescent probes, and everything's run in the 384 micro titer well plates, so the amounts of reagents – the license fee that you have to pay for the technology is very low. So the running costs of the machine are actually quite low, but the initial investment is exorbitant. So we anticipate that this machine will be limited at the moment to assigning values to reference materials, and we look forward to working with Jennifer and her

colleagues at that Immune Tolerance Institute, because now we have two laboratories that we can bounce off each other and make sure that we are coming up with common values.

>> Rebecca Buckley:

Thank you.

>> Rodney Howell:

Thanks very much, Bob. We need to move on, I think, now and hear from Dr. Duane Alexander, who is the director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. And Duane and his colleagues have been discussing how the NIH might be helpful in assisting with some of the proposed pilots that [inaudible] SCID. Duane?

>> Duane Alexander:

Thanks, Rod. This will not be a very long presentation. It's really to follow up on the discussions that we had at the last meeting. One at these days, I'm maybe going to learn that things always take longer to do then I expected when I first talk about them. My kids can attest to that, because I was always telling them that chores would only just take 10 or 15 minutes to do, and they wound up working for over an hour. So it's a longstanding problem that I have.

Anyway, the discussion – this comment on the – part of the discussion we had at the last meeting about getting more cases screened for SCID than we were getting from just the two States where it was being done at the time. The importance of this was that we have a disorder that has an incidence of 1 in 100,000, and we had screened so far over 60,000 babies and had not come up with one case. So it became clear that the rate-limiting step was the number of kids whom we were able to screen in getting enough information to make a decision on whether this was ready for universal use. So I made a statement at that time that this could be something that we might work on, with the Newborn Screening Translational Research Network that we had just funded, coordinated by the American College of Medical Genetics. And we thought that this might not take too long.

Well, that's where I was wrong. We've made progress, but we're not finished, partly because this is the first project to be brought to the new network. We have met with Mike Watson and his staff. We've talked about how to do this – how to work through the contract process and procedures to make it a possibility available to the people participating; make a selection of who would be doing this – maybe reach agreement on exactly what the protocol would be, like the ones that are already in place; and find a way to provide the funds to the sites that were going to do the work. This would be further complicated because it would be extra amount of Federal funds and private funds, because the Jeffrey Modell Foundation, which focuses on immunodeficiency disorders, had made an offer to provide some co-funding – extensive co-funding for the sites that would be doing this to help cover the – augment the Federal dollars to cover the cost. And so the questions really revolve around how to transfer funds to the sites that were selected and allowing – and to do that in the fastest and most efficient way.

Well, I can just say in a nutshell that we're still working on that. We're working through the intricacies of contract requirements and funds transfers and the whole process of getting this done. We will get it done, and we will get it done as quickly as we can, and we'll report to you – we'll let you know, actually, before your next meeting just how we've gotten this done and where it's going to be done and so forth. So that's about all I have in terms of concrete offer – information offer right now.

>> Rodney Howell:

Any questions of Dr. Alexander?

>> Robert Vogt:

Rodney, this is Bob Vogt. May I just ask one point, please?

>> Rodney Howell:

By all means.

>> Robert Vogt:

Duane, I just wanted you to know and the committee to know, I've had discussions with Fred Modell about the funding, and we refer to the, quote, "Wisconsin model," which was to get the assay up and running for about a half a million dollars, and that included a first round of general population screening. What I told Fred – and I think he was a little surprised by this – is that when you go to a large State, it's going to cost more to actually get the numbers if the point of this is to get numbers and find cases, which obviously it is. So I just wanted to mention that I think there's some sense that a half-million dollars would get you California or New York, and I'm quite sure that's not the case. Do you all have a sense of magnitude as far as what your funding level might be for a large State?

>> Duane Alexander:

Yeah. What we would have to do would be to combine dollars and contracts, add additional dollars to them, and put the money from the Modell Foundation – what they're offering – all together in order to get the size that we need. And we don't know yet whether this would be one large State, two large States, several smaller States – whatever. So – but we do recognize that – you know, that there is a cost per patient screened that you just can't get away from in addition to the setup and startup costs. So it's not a cheap operation.

>> Robert Vogt:

Thank you, Duane.

>> Rodney Howell:

Obviously, one of the questions will be to discuss and discover what it would really cost to do one of the large States, and I don't think that's yet come. One of the things that we should, as a committee, discuss is how we will solicit and receive information such as the SCID activity and whoever's – there's been a number of people that have come forth with interest in SCID. But we will have recommendations on virtually everything that comes before this committee about areas that need additional study and so forth. And I wonder if members of the committee would like to comment about how we, as a committee, should be involved with these as they go forth. We know that we have – in our letter, we had said, "We would like you to get this information and then come back to the committee," so I think that's clearly stated. But I guess the question that's in the middle of that is, "What is the role of the committee between identifying holes or – in the evidence that we think are holes in the evidence and being of assistance or help to the various and sundry people who would like to receive that?" Can we have any comments about that?

>> Michael Skeels:

Rod, this is Mike Skeels. I'm not sure if this is – addresses the question you just asked or not, but it seems like, having reviewed a given disorder and its nomination and come up with gaps and additional information that's needed and so forth, we should ask people who want to approach our community to really focus on those gaps that we've identified. I mean, for example, what we really need to know from these pilots in Wisconsin and Massachusetts is, first of all, is whether or not a TREC assay can be operationalized in a high-throughput environment, but I actually have no doubt that it can be. But not only that – what's the cost-benefit associated with screening a population? We've got a combination of low incidence and very high cost of treatment for SCID, which were actually two of the main factors in our committee deciding not to take SCID forward. So I think we need to make sure that people know what it is that we've identified as the existing gaps in information rather than just sort of bombarding us with all kinds of new information that we may not think is the highest priority.

>> Rodney Howell:

Well, I think that the letter that we sent certainly has those gaps spelled out that we identified as gaps. Peter, I wonder if I could ask you a question about the newly funded – the newly passed Newborn Screening Saves Lives Act and whether or not there are – is any funding in mechanisms within HRSA that could be helpful to address some of these gaps that we're identifying.

>> Peter van Dyck:

Well, the money has specific guidelines, and it would not be available for research-type activities. While it is generally speaking educational and service money, I think for a specific research [inaudible].

>> Rodney Howell:

So specific research, but it might be available to a State that was establishing information about informed consent or things of that nature that we [inaudible], as long as it was clearly not a research effort?

>> Peter van Dyck:

Well, I don't have the exact language in front of me, but generally speaking, for grants of the State, for groups of States, for education and service activities.

>> Rodney Howell:

Okay. So I think that they –

>> Peter van Dyck:

And for operation of the committee.

>> Rodney Howell:

Right, exactly. So apologies to the committee. We have one – a large table with one phone that keeps going back and forth. But the bottom line is that it would appear, then, that although certain of these funds might be helpful for some infrastructure assistance, basically when you're talking about research, you're going to be looking at, perhaps, and developing tests and so forth. You're going to be looking to the CDC, the National Institutes of Health, and perhaps private funding. Is that basically how you see that coming? Does the community have any specific wisdom or comments on this subject? I think we'll have to continue to find our way along and so forth, but I'm pleased that a number of members have come forth with specific ideas that may help move the – some of – help build some of those gaps in the SCID thing. Michele, did you have any comments?

>> Michele Lloyd-Puryear:

Well, I wanted to know if the committee felt it would be important to develop a work plan or an action plan after each nomination so that there was some mechanism that the committee was following – that particular condition and the evidence for that condition, if the committee thought that would be useful. Is it increased work without a huge benefit. I think that we need to make clear what our expectations are for additional information and let other people bring it to us.

>> Gerard Vockley:

Yeah, this is Jerry Vockley. I agree. I don't think we want to get into micromanaging this. I think we set out a series of – our list of gaps. I would be in favor of saying to the nominators, "Bring it back when you think you have those still." Now, obviously, if they would like to have some feedback on it, they could talk to Rod or Michele or the primary reviewer on the evidence

review, or I – we could designate somebody to perhaps be a touch person for that. But I don't think we want to get into micromanaging.

>> Rodney Howell:

That's kind of my sense, too. And I think on the other hand is that certain members of the committee, because of their other – of their day job, shall we say, might be able to be helpful to various people, as far as helping identify funding and so forth. And I think that would just come as a national responsibility, not necessarily of the committee member, but because of the work that they do ordinarily.

Any further comments about that? Thank you very much. So it sounds like some action is happening to help Jennifer, the nominator, and her folks fill these gaps. And so, hopefully, we can see some progress there, and hopefully we'll hear some specific progress before we meet next time. I certainly hope so. Any further comments about the SCID?

Let's move on to our next topic – we're right on time; congratulations – the residual bloodspot proposal for a briefing paper on the topic of policies and procedures where they're used in storage. And we're going to hear from our committee member, Jana Monaco, and from Dr. Brad Therrell. And this proposal came up after our session in February, where we discussed residual bloodspots. As you know, the issue of residual bloodspots is starting to receive – it's not starting to receive; it's getting a tremendous amount of public attention. And it is something that we need to be very, very attentive to. And there is a recent article – it was in Science – that was published by Jennifer Couzin-Frankel. There's also, on your Internet site today, a press release from the American College of Medical Genetics about the importance of the dried bloodspots. But we – I would like now to ask Jana and Brad to give us a draft outline for a big briefing paper that they're looking to do that would provide guidance to this committee on the policies and procedures for the retention and use of residual dried bloodspot material following newborn screening. Brad? Jana? And you all should see their PowerPoint slides coming up.

>> Jana Monaco:

Can you hear me?

>> Rodney Howell:

Crystal clear. Yes, we can hear you well.

>> Jana Monaco:

Okay, great.

>> Rodney Howell:

And Brad, I assume, is there, too.

>> Bradford Therrell:

Yeah, can you hear me?

>> Rodney Howell:

Perfectly.

>> Bradford Therrell:

Good.

>> Jana Monaco:

Okay. Is that better now?

>> Rodney Howell:

Oh, yes. It's just your gentle voice.

>> Jana Monaco:

Okay, I had speaker phone. Sorry.

Okay. As we mentioned, our presentation came from a variety of reasons. And our group was tasked with that – with providing a draft outline for a briefing paper to States that provides guidance from the advisory committee on policies and procedures for the retention and use of residual dried bloodspot material following newborn screening.

I'll tell you briefly about our – the members of our group. Dr. Harry Hannon and Dr. Brad Therrell are the ones who provided one of the presentations during the February meeting that was just referenced by you, Dr. Howell. And their research for that presentation, "Storage, Retention, and Use of Residual Dried Bloodspots," and their wish to update their 1996 report, "Guidelines for the Retention, Use, and Storage of Residual Dried Bloodspot Samples After Newport Screening Analysis: Statement of the Council of Regional Networks for Genetic Services," (CORN) provided the basis for our outline. Dr. Don Bailey of the Research Triangle Institute has provided some insight as a parent advocate and as someone who has published research on the consent process that we've [inaudible]. I have been involved as a parent advocate and also as a member of the Secretary Advisory Committee. Alaina Harris from HRSA is there to help keep us on track.

So at this time, I will turn the presentation over to Brad so that he can provide you with the outline of our proposed white paper.

>> Bradford Therrell:

Thanks, Jana.

>> Jana Monaco:

Thank you.

>> Bradford Therrell:

So, on your screen, hopefully, you have the first slide, which shows us some history of this in terms of publications. There are always some publications coming out these days on the stability of DNA and dried bloodspots. And I've just highlighted here a couple – this is a 2005 publication talking about stability studies and showing that DNA can be detected from bloodspots for certain things for at least 11 years. And in 2008, a report saying, well, storing for 25 years even without air conditioning was okay for what we were doing. Likewise, the 2009 publication talking about abrasive – slightly abrasive contact between the specimens can result in some cross-contamination, but while you can detect it, it usually doesn't affect most routine molecular genetic assays. So there's a lot of work going on in terms of getting DNA out of filter paper, and you see these kinds of papers are all tabbed. Now, Jana mentioned that back in 1996, we issued a report on this – we as a committee – from CORN, and we noted at that time that there was stability issues – that stability was likely okay for some things and not okay for others, and that has certainly been borne out.

Now, stability is not the only issue. The big issue is consent. And I have a quote here at the top that residual newborns' dried bloodspots have been taking on – have taken on a new life as a result of developments in genetics and increasing ability of bioinformatics to link DNA information with clinical data. And that's certainly true, and that's where we're getting into some issues, because the specimens, when they're generally collected, are not necessarily done with consent, and not necessarily are people informed that there are possibilities to do other things like research on the new specimens. So in 1996, we pointed out again that appropriate consent would be an important issue, and some legal experts have proposed that it's impossible to get that kind of consent, so it's just not possible to adequately inform or educate parents about all the potential uses of their bloodspots.

The 2000 report from the AAP task force noted that we should develop some model consent forms and informational materials for parental permission for the use of the newborn screening samples, and that we should develop educational materials for parents that include information regarding the storage and use of residual samples. So we've known for a while that we're going to get into this issue, and now we're there.

The 2004 publication – and that's actually where the quote at the top of the page comes from – talks about the need to be transparent, to have strict rules for scientific study, and so on. And now, here we are in 2009 in Austin, Texas, my own city – a newspaper article talking about medical privacy advocates – ethicists saying that parents should be asked for consent before newborn screening samples are kept. And indeed, you're aware that there are at least two lawsuits ongoing right now about sample storage issues.

So with that as a background, Harry and I put together some preliminary information and then involved Jana and Don and Alaina and – looking at how we're approaching this in order to provide you with an outline that we think would work in terms of updating the committee and the literature on what's going on, and then coming forward with some recommendations from the committee. So the thesis for this article would be that dried bloodspots remaining after newborn screening has been completed are valuable resources and should be carefully and thoughtfully preserved and used for public health benefit. And we emphasize public health benefit here because they were collected in the first place for public health benefit, and that's where they should be used in the end.

Now, the idea is for me to go through this outline and then have you discuss and tell us whether we're on the right track, whether we're too broad or too narrow, and so on. So here we go. So that would be the thesis; then the approach would be to develop national guidance policy for attaining and using dried bloodspots that remain after newborn screening is completed, and this would presumably come from the committee.

So just to give you a little more background, we updated what States are doing with their bloodspots right now. And you can see from this graph that there are sort of two schools of thought. One school are the ones that save it forever for research, and that's about 54 percent of the newborn population being stored for greater than 18 years. The rest of the population, 46 percent, is stored for less than 3 years. But there's this big gap in the middle: either you save them for up to 3 years or you save them forever, essentially. And so it's a split; it's about a 50-50 split. And so we're going to have to think about that as we go through this.

So we've develop the outline in four stages, and I'll just sort of run through the stages. And you've got copies of these slides; I won't dwell on two many of them. But there are basically four divisions. We're going to talk about scientific issues, policy issues, financial issues, and then legal/ethical issues, and then we'll end up with having a lot of background references.

So in terms of scientific issues, we'll talk about – in the paper, we would talk about physical limitations, looking at blood volume, specimen quality, looking at biomarker stability. We would talk about the retention processes that are being used, looking at examples of what sorts of permissions and information are out there. And we noted here that there are only 12 programs that mention storage in their educational materials at this time. We would look at the definition that programs are using for purpose, including the primary goal of program quality assurance and program improvement; and then the secondary goal, the family issues, program research and nonprogram research. We would also then look at retention conditions; we would look at retention duration, looking at the period of time, and whether or not States are requiring additional permission for this, and what the models are there. We'd look at space requirements. We'd look at accessibility in terms of computerized systems and noncomputerized systems, and we'd look at how specimens are disposed of in the end – that is, whether the identifiers are removed or not and how they are identified in terms of hazards. Other scientific issues would include the usage process, so we'll look again at the program needs in terms of true cases for quality improvement and method validation, looking at the parental request for other things that parents might need or want done, and looking at research with identified and de-identified models being reported. We would look at accountability – that is to say, the samples that are

released – who the samples are released to, what tracking is there, and whose property they are, and how they're disposed of in terms of returning or not returning – and look at some of the legal requests that are – uses that are being made of forensic and others.

In terms of policy issues, we would review the general interest concerns, the questions that need to be answered, what the policymaker's responsibilities are in terms of public trust and transparency, what sort of privacy protection issues there are in terms of parent advocacy requirements and legal requirements. We would look at what the State's responsibility is, in terms of public trust and transparency and privacy protection. We would look at what the Federal responsibility is in terms of this committee and other Federal agencies. And we would look to what other policy guidance is available, so we would search and find out what policies are out there and bring them to you to review and learn from. So we know for sure that there are at least two out there, one from the Association for Public Health Laboratories and one from the American College of Medical Genetics. We would also give you examples of model working repositories, such as the honest broker system that's being used in Michigan; South Carolina has a different sort of protocol; Minnesota, Missouri, and so on.

Then financial issues – we would look at cost and value questions. So we'd look at education, because we think that that's a big part of this, and there's going to have to be parental education and policymaker education – see what value there is and what the process is and how much it costs, looking at what the costs are for bloodspot collection kit modifications that might be necessary if we get into the retention use issues in States that don't currently address that; looking at the cost for a storage program, for program use for quality assurance and then for research; looking at the cost of accessing the specimens in terms of the computerized processes; looking at the cost of shipping for research purposes; looking at the cost of other researchers and for storage and confidentiality; and then any other financial issues that we can come up with.

In terms of legal and ethical issues, we would look at the issues regarding ownership, stewardship – and we note here that there are 15 States that actually address issues about storage and use in their statutes at the current time. We would look at privacy protections. We'd look at awareness and education for parents and the public. We would look at the communications that are taking place in terms of consent and dissent. And especially, we would draw on some of the work that Don Bailey's doing on his projects with Fragile X – looking at sensitivity, understanding, education, and culture; looking also then at legal backup or whether States actually have government attorneys that are aware of what's going on – how well they're educated – and are they available to get into these issues?

And then we would see the final part of this paper being recommendations from the committee in terms of national policy, and they might take on the following aspects. You might have a recommendation regarding parent educational material and give some models for State use. You might have models of consent and dissent processes and whether you want to take a stance on either – consent or dissent is a question that you'll have to address. And you may want to take a position on public-private partnerships in terms of public health departments, how they will interact with advocacy groups, and how they interact with researchers, and how companies might be involved in this, because all of these people consider themselves stakeholders in dried bloodspot storage and use. And then finally, you might want to take a position on national

repositories in terms of virtual or real, whether there should be State, multi-State, regional, or national or whether some combinations of these might be better served. And finally we would end up with extensive references for you to review and use.

And that's pretty much the way we see the paper going. Again, it's up to you as to whether you want to do this, number one; and number two, how detailed you want us to be in terms of the issues that we've raised here today. So with that, I think we can have some discussion.

>> Rodney Howell:

Thank you, Brad. Jana, do you have any comments?

>> Jana Monaco:

No, we had good discussions on this, and I think Brad pretty much covered it.

>> Rodney Howell:

Then I don't think there are many issues that are of greater importance to the committee to think about at the current time, because I think that if we are not clear about the value of the dried bloodspot, then – if we don't or are not able to reassure the public of their value and of the fact that they are being very properly and carefully stored with great control and so forth to protect the privacy and so forth, I think it could significantly undermine the newborn screening program, because they've been extremely valuable resources.

Having said that, I would like to hear comments from the committee about – I think the key thing is that – would you like to see this group proceed to do a document that – and draft document for the committee to review? And can we have some comments from the group?

>> Ned Calonge:

Brad, this is Ned Calonge. I wonder if I could ask just a couple of clarifying questions. For the States that are currently doing this, do they keep identifying information, or is there a mixture? Because part of the issue is how much information accompanies the bloodspots and if uses for things like prevalence or other issues versus trying to link the spot with an adult or an older child at some later stage – I think the issues are different.

>> Bradford Therrell:

Yeah, I think that all programs that I'm aware of, and I may be wrong, but I think all keep them linked to a certain degree at the beginning. And so, what most of them would do is have a serial number on the form that has the blood on it so that's the link. And then the information that connects to that serial number is kept in a computer somewhere else. Now, those specimens are stored, and that's the way they're retrieved, and all the information is linkable. When a researcher comes and makes a request, then, that usually goes to an IRB, and the IRB determines whether or not it's a valid request and whether or not there needs – and the researcher would

have asked this – whether or not there would be linking or non-linking information. And if it's going to be not linked, then it would be randomized and given to the researcher with no identification – no identifying marks at all.

>> Ned Calonge:

Thanks, Brad. If I could just ask one other question, then I'll listen some more. The places that have consent or absent – so they've actually put into place cost-effective methods where they can keep some and throw out others?

>> Bradford Therrell:

We're going to be looking at that. We've got some information on what's going on in Michigan, what's going on in South Carolina, what's going on in Minnesota, but we don't – we haven't gotten into the details. So whether or not that's cost-effective or not and whether or not – how that's working, we're going to research that and let you know.

>> Ned Calonge:

Okay.

>> Bradford Therrell:

Because there are some models out there that are in place.

>> Ned Calonge:

I guess – you know, Colorado is home of the black helicopters, and I think this is going to be a tough sell. But I think this is important work, and I think it's something that the committee should take on.

>> Piero Rinaldo:

This is Piero Rinaldo. I have a question for Brad and for Jana. I'm looking back at your slide #10, the one that says "Scientific Issues, 3 of 3." And I'm wondering if what you think about trying to also have a more detailed distinction between what people perceive as research issues versus what is method and validation issues, because this is certainly one of the big sort of issues, at least here in Minnesota, about – that anything done is labeled, often in a negative – with a negative connotation, as "research." I think that, you know, you do mention method validation. But I think that an important part of this document, which, like Ned, I think is essential, that moves forward is to really explain how important it is to really develop and validate robust assays, where you really don't get surprises when you go into a high-throughput node. So it's more of a suggestion, not a question really, but I think that it has to be addressed as a separate, independent, and yet very important aspect of the use of the residual bloodspots after newborn screening has been completed.

>> Bradford Therrell:

Yeah, I absolutely agree with you, Piero, and that would be our intent to break those things out. This is just a general outline right now, but I appreciate that input.

>> Coleen Boyle:

This is Coleen. I was looking at the exact same slide that Piero was looking at. And Jana and Brad, I really think you did a great job outlining an obviously very important but challenging issue. And I guess I'm not clear – are you going to try to define what you think are sort of the – your thesis in the beginning, which is public health benefit – "What are the potential public health benefits from both a programmatic standpoint as well as a research standpoint?" – or are you just going to sort of do more of sort of a listing of the potential public health benefits? I guess I'm trying to say – where this paper's going in that?

>> Bradford Therrell:

Right. The idea was for you to tell us what you prefer. We can do what ever you want. We're doing this for the committee, not for our own benefit.

>> Coleen Boyle:

Okay, fine. I guess –what are your thoughts, Brad?

>> Bradford Therrell:

Yeah, well, I think we would approach it from the point of view of – if you don't tell us differently – that we would approach it from the public health point of view and try to give you examples of how this has been beneficial and how it would be beneficial in public health interest rather than just list out –

>> Coleen Boyle:

I guess I was thinking of – yeah, I mean, I would probably – maybe you can go a little further in terms of providing some guidance.

>> Bradford Therrell:

So that was an initial question that we had.

>> Coleen Boyle:

And I'd be interested in the committee members' thoughts on that.

>> Bradford Therrell:

When we were first discussing this with Michele, she was actually interested in keeping this fairly short. And when Harry and I and the rest of the group got to talking about it, we ended up with a little more of – a little more pages than what she originally intended. So that would be the question, you know: "How detailed do you what this sort of a paper to be?" And we felt like it couldn't be just highlights. It had to be some details. And that's why it came out sort of long.

>> Rodney Howell:

I don't think it should be vast, but it should be substantive, because I think this is going to be a very, very important paper.

>> Michael Skeels:

Say, Brad, this is Mike Skeels. I think Coleen just made a great point. The word – I don't need to put words in your mouth, Coleen, but "benefit" is a loaded word and a relative word, and some people would think that screening all newborns for chlorates or all other environmental chemicals is a public health benefit, and that's not proven at all. So I think you're on pretty thin ice if you start with the premise that you're going to find what is a public health benefit and then go from there. I would encourage you to be pretty narrow with that rather than broad.

>> Bradford Therrell:

Okay.

>> Michael Skeels:

That's just my opinion. I also want to say, as I believe Ned already said, how great it is that you're doing this. I think this is badly needed. And those of us who have sort of shied away from saving our samples over the years, I think, largely have done so just out of fear that we're not going to be able to deal with these very issues that you've identified. You know, if we can ask, "Can you do this?", we're not going to know how to answer, so we've been very conservative. And I think that's made these samples less available than perhaps they should be.

>> Bradford Therrell:

Yeah. I mean, one of the things that we think would be important is this issue about education, because I think that most people would not have a problem as long as they were educated up front and they were asked for their consent. And that's what we don't do right now.

>> Jane Getchell:

Brad, this is Jane. So you will be addressing the whole issue of informed consent?

>> Bradford Therrell:

We will address it, and what position the committee wants to take is another issue.

>> Rebecca Buckley:

This is Rebecca Buckley. Can I ask a question relevant to that? I like your graph about how many save the specimens for more than 3 years. Do you know how many of the States currently have informed consent?

>> Bradford Therrell:

Well, there are three programs that claim to have informed consent: Maryland, Wyoming, and the District of Columbia. But in fact, if you check in those States, it seems it doesn't work any different from the ones that have dissent. That is, they get somebody to sign the form, but it's usually done in the packet when they enter the hospital, and nobody remembers ever having done it.

>> Harry Hannon:

Brad, she's asking the question about how many have consent to store the samples.

>> Bradford Therrell:

Yeah, that's a different question, and the answer to that one is that that's where Minnesota and South Carolina and Michigan are serving as sort of models right now. That was Dr. Hannon, by the way. He's on the phone as well.

>> :

Separate consent when they collect the spot and then another consent to store it – is that what you're saying?

>> Bradford Therrell:

Well, I'm saying that's one way people are looking at it, yes.

>> :

Well – and actually, what I heard from Michigan, they do not get consent to do testing. They do get informed consent to store it.

>> Bradford Therrell:

Right. And actually, in the case of Minnesota, I believe – you can correct me if I'm wrong, Piero, but right now, there's a proposition– there are some people who actually want the results thrown away as well as the specimens. After 2 years, they what the specimen and the results thrown out.

>> Piero Rinaldo:

Actually, there is already a variant of that in place, and that is, a parent can – or guardian or parent can ask to destroy any evidence that the test was completed. So even if we have a totally, you know, pretty simple comment that says, "This sample – everything was normal," they have now the legal right to ask that we go in and pretty much hack our own laboratory information system and delete the results. So instead of the report, we'll have a sentence that says, quote, "Pursuant to this code of" yadda-yadda "the law, this was [inaudible] been deleted." You know, we try to argue about, you know, the foolishness almost of this, but there's no way. It might even go forward, because they might actually want to go in and – you know, in whatever software database and physically destroy every individual analyte result. That hasn't happened yet, but it's on the laundry list of the so-called privacy advocate.

>> Rodney Howell:

Well, it just emphasizes the need for this paper to be put out for the public so the public has a better understanding and so forth. Further comments about this? I hear a great deal of support for this. The other issue is that, obviously, some very thoughtful families in these States that discarded them immediately might want their child samples stored. And have you thought about a national site where a family might request this – the baby's sample be sent so it could be kept in perpetuity?

>> Bradford Therrell:

Well, we've talked a little bit about that, and that was a part of the ACMG's policy statement. But that's going to be an issue for States, because I think States are going to look at that somewhat as an unfunded mandate if they've got to worry about accounting for the specimens and then sending them off somewhere and making sure everybody knows what's going on. So we'll certainly bring that up.

>> Rodney Howell:

An alternative: The family could get the sample and mail it in themselves.

>> Bradford Therrell:

And that happens right now in most programs.

>> Rodney Howell:

Are there further comments about – I hear a consensus on the telephone that this is important and that we should request that this group continue this. Is that the sense of the committee?

>> Christopher Kus:

This is Chris Kus. Yeah, I think that's what I'm hearing, too. But Brad, will you be looking at international experience in this area?

>> Bradford Therrell:

Yes.

>> Rodney Howell:

Yes, I would hope so.

>> Sharon Terry:

And this is Sharon Terry. Can I make one comment? I'd also like to see the broader coalition be involved in looking at putting this together, so SACGHS and OHRP and some of the professional societies that might not be yet around the table, including maybe some of the other consumer [inaudible] sorts of groups.

>> Rodney Howell:

Well, I think that's – Sharon, I think that's an interesting area, but I think that this would be a report of this committee, and as such, I think that we should try to get a document together and then work with everybody else to have comments. We obviously will put the draft out for comment.

>> Bradford Therrell:

Our intent right now would be for this small group to work on this paper and have it ready for you for your next meeting.

>> Rodney Howell:

Let me make a couple suggestions. Number one is, I think that we – that I should really identify this as an official workgroup, and we'll call it the Dried Bloodspot Workgroup, which seemed like an appropriate title and so forth. And I think that this is a great group to work on. I'd like to suggest you add a couple souls to it – that's – up from the committee, in view of the issues that have to do with – the ethical issues – best to add Alan Fleischman if we could to your group. And I think it'd be helpful if we could get Norgaard Pedersen to join the group to add some international experience and so forth. And I think that an attorney who's expert in the area would be very helpful. Have you thought about that in your drafting of a document?

>> Bradford Therrell:

No, but we will discuss it with Michele and –

>> Rodney Howell:

And I would suggest that one attorney who's very experienced in genetics and thinks about these things is someone like Lynn Fleisher, but that's – we can discuss that. But we'll – if we could then have this workgroup – and then you'll plan to have a draft fairly soon, right?

>> Bradford Therrell:

Right.

>> Rodney Howell:

And then the – my note suggests that you would have a Webinar that you might have during the summer – that you could present this paper to various stakeholders, and that's very important. I think that Sharon has pointed out that we need to get certainly the Genetic Alliance involved in that, the newborn screening programs, pediatricians, the other genetic groups and committees, public health professionals, and so forth, etc.

>> Sharon Terry:

And Rod, this is Sharon. Could I volunteer for the workgroup part? Because Genetic Alliance has been working a lot on the privacy issues, because that concerns us a great deal, very broadly as well as very specifically, around this.

>> Rodney Howell:

We never turn down good workers. That would be excellent. Thank you, Sharon.

And then, I would like to see a final draft of this before the committee in September at our meeting. Can we do that?

>> Bradford Therrell:

That's our plan.

>> Rodney Howell:

Okay. And then having heard from – and there'll be a lot of comments about this. This will be an extremely visible work, because most of us – I think all of us are on the newborn screening blogs, and virtually all the blogs are consumed with – concerned about how some of these samples are stored and used. And I think a lot of that comes because folks have not been properly educated and really have concerns that are not terribly warranted. And I think it'd be important to establish a clear line of thought. Michele, you had a comment.

>> Michele Lloyd-Puryear:

Well, just that the Secretary of the Advisory Committee on Genetics, Health, and Society that you spoke at, Rod, expressed an interest. We had raised this issue, or you did, as an important

issue the committee was looking at. And they expressed an interest in working with it on this issue. So would you like us to invite that committee to the meeting in September along with OHRP?

>> Rodney Howell:

I would have the – again, I think many of you know I spoke recently to the Secretary's Advisory Committee about the work of this committee. There was a specifically expressed interest in having the committee involved, as Sharon has pointed out and so forth. So perhaps we can invite them to come to our September meeting, if that's good with you, and OHRP also.

>> Michele Lloyd-Puryear:

Okay.

>> Michael Skeels:

So Brad, this is –

>> Rodney Howell:

Let's have a big room.

>> Michael Skeels:

I'm sorry, Rod; this is Mike Skeels again. I just have one more question for Brad before we leave this. Have there been any examples of State newborn screening programs doing things on maybe a large scale with these bloodspots that were considered to be abusive or unethical? I mean –

>> Bradford Therrell:

Not a single case has been reported that I know of.

>> Michael Skeels:

Yeah. I mean, Cary Harding is in the room here; he was just asking that question. I didn't know the answer; I couldn't think of one. But I think that it's important to put into your report as well – that it's not like there's some giant ethical problem we are trying to solve here.

>> Bradford Therrell:

Right, absolutely.

>> Michael Skeels:

Thank you.

>> Rodney Howell:

Thank you very much. I think this will be a very important paper, and I commend you on your draft and so forth. Does anyone else have any comments? Peter, any comments before we move on?

>> Peter van Dyck:

[Inaudible]

>> Rodney Howell:

Great enthusiasm. And I think that we will want to have a document that we can widely publicize and that will also be helpful in understanding this process.

We're right on the moment, and I'd like to move on now to discuss the impact of the present economy on the newborn screening infrastructure. And we're pleased to have Jane Getchell, who's a committee representative. And as I think you know, Jane represents the APHL, and she also importantly is director of the Delaware Public Health Laboratory. So she can tell us exactly what's happening. Jane?

>> Jane Getchell:

Thank you, Dr. Howell. Yes, I am going to describe the impact that the current economic climate has had on newborn systems. And I want to begin by acknowledging those who – all of us worked together on preparing this presentation: Brad Therrell, Jelili Ojudu, and Chris Kus. So thanks to you folks as well.

This first slide you probably have seen before, although this is an update as of May 1. It shows how many conditions are required in each of the different newborn screening programs. And those with the highest number of conditions screened for are in the raspberry color, 40–49 disorders are the purple color, blue would be the 30–39 disorders, and then finally orange is 20–29 disorders. The numbers in circle represent those programs – those States that are providing all of the 29 core disorders. You know, I – what struck me about this slide was – comparing it to a slide that might have been produced 3 of 4 years ago – is the tremendous increase in the number of conditions screened for across the country, even though obviously there are differences among States still.

Before we can talk about the economic impact, we need to understand a little bit about financing of newborn screening systems in States. It's different in every State, and generally States have multiple sources of funds that paid for the newborn screening, testing, and follow-up programs. Funds can come from State appropriations, from program fees, and from grants and Title V. Another aspect that's different from State to State is the way those fees are collected. Generally, States will sell kits; this is the newborn screening collection forms. However, there are some States that bill insurance and Medicaid directly, and others – Delaware, for example – bill

hospital. Medicare reimbursement will vary from State to State, so it depends a lot how much a State is able to receive from Medicaid imbursement.

What the fees are used for also varies from State to State. Almost always, the fee does cover the laboratory cost, and usually it covers some of the follow-up cost. But it may not cover all of the follow-up cost. It may or may not cover education of physicians, of specimen collectors, of the public, of parents. And it may or may not cover the treatment: special formulas, special foods. Generally, the initial fee that's charged covers any repeat testing that is requested by the program to sort out initial screening results. In those States that are mandatory to screen States, usually the initial fee covers both the initial and the second screen, though that isn't universally true.

This slide really is a different representation of the very first slide: going from left to right, the number of mandated tests in each State's program. You have – starting with New Jersey, with something like 24 tests on the far left, going all the way over to South Dakota on the far right, with 54 mandated tests. Now I'm going to overlay on that the program fees that are charged by each of these different programs. And first of all, you'll see there is really no correlation in the amount of the fee that's charged and the number of mandated tests. So, for example, if you look at South Dakota, which offers or provides 54 mandated tests, it has one of the lower newborn screening fees. The other thing I want to point out on this slide: There are, in fact, three States as well as the District of Columbia that don't charge any fees.

Now – and as for how we obtained information from States, we wanted to know how the economic downturn was affecting their newborn screening systems. So we put our heads together, and we developed a series of questions to ask of the different newborn screening systems. We reviewed those questions, we piloted the questions, and then we modified them based on the results of our pilot. Then we e-mailed the questions to newborn screening laboratory managers, to newborn screening follow-up coordinators, and also to state laboratory directors. At the end of the week, I'm pleased to say, we had received responses from 35 programs. Those programs that didn't respond, we sent a follow-up e-mail to, and that ended up with a – final responses from 47 different programs. So we were quite pleased with the response rate.

The questions that we asked: first of all, "Has the current economic climate affected your newborn screening program's (a) ability to travel to meetings, workshops, and seminars; (b) your personnel, whether it's a hiring freeze or staff reductions or something else; (c) has it affected your newborn screening panels? Are you able to add conditions? Have you had to eliminate conditions?" and so forth. "Has it affected the number of days that you operate your newborn screening laboratory? And are there other impacts that the economy has had on your newborn screening system?"

All right. In answer to our "travel to meetings, workshops, and seminars" question, 37 newborn screening systems said, "Yes, the economic downturn has impacted our ability to travel to meetings." Nine said no. In fact, seven States have no out-of-State travel, and that would include Delaware. Most other States have restrictions of one sort or another. Generally, it's limitations on the number of people who can travel. It's the process for obtaining approval to travel. And interestingly, these limitations/challenges are regardless of the funding source. It doesn't matter

if it's State funding; it's grant funding; or even, in many cases, if it's direct funded by, for example, ACMG. I have to take vacation to go to these meetings.

Some other examples: Hawaii travel approval requires the governor's agreement. Georgia said it can take them up to 60 days to get travel approved. And Colorado was another State that, regardless of the payer, their travel is severely restricted.

Looking at personnel and the effects on personnel of the economic climate, 35 programs said yes, it has affected personnel; 12 said no. In fact, 60 percent of States are currently undergoing a hiring freeze. And I can tell you, in Delaware, we have been under a hiring freeze for the last year. Fortunately, we've had only one person retire from our newborn screening program, and we were able to move somebody from our virology lab into newborn screening. We are also down a genetic counselor.

The other thing that I think affects personnel and personnel time is the States that have furloughs and pay cuts. Of course, if you're furloughed, you're not there to do the work, so that does effectively reduce the staff. And in Delaware, our governor has proposed an 8 percent pay cut. And I suppose if you're the newborn screening program, the good part about that is, there's no furlough to go along with it, so we won't be down in personnel because of furlough.

What about the effect of the economic climate on newborn screening panels? Eight newborn screening systems said yes, it has affected their newborn screening panels; 36 said no; 2 said maybe; and 1 didn't know yet. Several programs reported challenges in adding new tests. Just a few comments: Florida, for example, said they were unlikely to add additional disorders if they were recommended. Texas, of course, has been trying to add cystic fibrosis, but as we understand it, there's still no money for startup. There's one State that is mandated to do LSDs, but again, there's no money to implement it.

Another thing I want to point out is the second screen question: For those States that have mandatory second screening, you wonder, "Do we want to continue this?" And this is a question that has come up here in Delaware, a mandatory second screen State. Hopefully we will be able to maintain our second screen, but we have already eliminated second screens on MS/MS.

In terms of the number of operational days, 6 States say, "Yes, the number of days has been impacted," and 41 said, "No, it has not." We talked about unpaid furlough days already and their effect in reducing manpower. Of course, I think California is probably the first program that we heard about with the 2 furlough days a month.

Another interesting program is the Utah. They have a mandated now 4-day, 10-hour-a-day workweek. As I understand it, though, they do have a skeleton crew that has been approved to work on the fifth day in newborn screening, so there was sort of an accommodation made, recognizing the importance of newborn screening.

Weekend work is in jeopardy, and certainly we have an example of one State, the State of Georgia, which no longer is working on Saturdays. I think, you know, States were trying to go to weekend work, and this has been put on hold as a result of the economic downturn.

Some other comments that we heard – disapprovals have been slowed greatly. We received a great deal of scrutiny from many levels in the hierarchy of our agencies and organizations. So it takes a long time to purchase equipment, if it's even possible. For those States that don't have a hiring freeze that are able to create new positions, even that process has been slowed down. You can imagine the difficulties now that State government is having in recruiting people, wondering, you know, what's going to happen here. The one good thing I have to say is, nobody told us of layoffs in either State government or in – certainly in newborn screening programs.

There have been other system improvements and training that's been delayed. Notably, the comments we heard had to do with upgrades to computer systems, advances in software, and so forth. And another area where system improvements have been put on hold is in the area of courier service. I wanted to say, we in Delaware have put on hold our molecular testing for cystic fibrosis.

So just to summarize what we learned, travel is severely curtailed, so we want to keep this in mind if programs are recommended. How are we going to get these people trained? Manpower is decreased, training is restricted, and program expansion right now is a challenge.

The other thing I want to say is, this is not business as usual right now. After 2001, those to me were the halcyon days of public health and newborn screening. But this is a temporary downturn, I think, for public health and public health laboratories and newborn screening programs. We will get through it, and certainly we've seen some encouraging signs. We are able to provide newborn screening still. But it just seemed important that we make the committee aware of the challenge that we're facing right now.

So we do have some suggested actions for the committee. First of all, continue to review the economic impact to State newborn screening programs as time passes. Secondly, it's important to consider the economic impact of committee core panel recommendations to States by requesting an economic impact statement. So we talked about this at our last face-to-face meeting as being very important. We need to know up front what the anticipated costs for implementing a new test would be – for implementing - really a new follow-up program as well. And finally, a suggestion not just for the committee but for those of us in public health and in States: We all need to work to raise the awareness within State health systems that newborn screening is critical and needs to be prioritized as an essential public health program so that when they're looking to save money and to cut costs, they don't look to our newborn screening programs.

Thank you very much. That's it.

>> Rodney Howell:

Thank you very much, Jane. Are there questions or comments for Jane about her very nice review?

>> Piero Rinaldo:

This is Piero Rinaldo. Jane, you briefly touched on the issue of the mandatory second test. And I wonder if that can be part of some more larger issue of – in a moment where the funding becomes tight, in the duration about revisiting existing practices to see if things could be done in a more effective and efficient way – in other words, how comfortable are you that, you know, there is no room for improvement for savings related to improving existing practices?

>> Jane Getchell:

You mean by eliminating the second test?

>> Piero Rinaldo:

Well, that is just one example, but, oh, we – I'm – you know that I am sort of partial for the discussion about performance. In other words, take, for example, States with relatively high false positive rates. It seems to me that by improving performance and by adding lower false positive rates that could be substantial savings in the overall cost of the screening and follow-up. So is that something that – is there a willingness to look into that and, say, perhaps to be able to, you know, survive the current challenging climate and perhaps even consider additions or expansions, don't you think it should be a reasonable strategy when you try to take a look in depth at current practices and see if things could be done perhaps in a more effective and efficient way – in other words, reducing the costs and improving value of existing programs.

>> Jane Getchell:

Yeah. Things about the second test: First of all, we do have the study of the value of the second test, at least for the endocrine disorders. And I don't think we have any results from that yet. And Harry, are you on the line?

>> Rodney Howell:

Harry was on earlier, and I was just getting ready to ask him the status of the second test study.

>> Harry Hannon:

I'm online, and we are working on it.

>> Jane Getchell:

Yeah. I mean, I hate to cut that off 'til we have demonstrated "Yes, second tests are good" or "No, they're not necessary." That was one thing, but the other thing, too, that I don't think that the folks at the State level who are making these suggestions and decisions understand is that this program has been based on two screens for years. And it's not something you can just turn off. In other words, yes, it's something we might look at, but it's something we would have to, you know, demonstrate, as you say, the quality, the consistency – redo our cutoffs and all that. And it's not something you can do quickly.

>> Piero Rinaldo:

Why redo the cutoffs? It doesn't seem too logical to me. Why should you redo your cutoffs?

>> Jane Getchell:

I think you certainly have to look at them, because you are screening using a very different algorithm.

>> Michael Skeels:

This is Mike Skeels, Piero. I agree with Jane completely on this. And I think it's a mistake for us to spend a lot of time on this committee trying to find ways to cut corners and save money in State screening programs when each of us has to make that decision independently. And many of us are operating high-throughput, extremely efficient programs as it is. We're able to do two samples in Oregon – by the way, there's an error on that one slide; it shows us that – $108 our testing; it's actually $54 for two tests. We're able to do two tests in Oregon for the complete panel for the price that many States are charging for one test. And I know there are a lot of us who have found every imaginable efficiency, and the idea that you can just ratchet down the number of false positives or eliminate the second sample or whatever is – I think, is really a blind alley. I –

>> Piero Rinaldo:

Yeah, well, we – this is something for discussion. But I think I really disagree with you on this, because the reality is that you are making statements based on no available evidence. Or at least evidence has not been made available for independent and objective review.

>> Michael Skeels:

You might want to read the literature, Piero. We've been publishing on this for about 20 years now.

>> Piero Rinaldo:

Well, I still don't know what your performance metrics are.

>> Jane Getchell:

You know, Piero, the funny thing is, I used to be with the Iowa program, and of course, Iowa is not a mandatory second screening State. I always wondered, "What are those States with two mandatory screens doing that – you know, that we're not, and what's the difference?" But you know, you have to be living in that State to really understand how it got to be where it is. It's a lot of history, and there's good science behind it, too.

>> Rodney Howell:

Let me bring up something. This – the question of the second sample came up very early in this committee, and Harry and his colleagues have been working on this for quite a long time. And Harry, do you have some ideas of when you might have a report on the second sample?

>> Harry Hannon:

We plan on having something for the September meeting.

>> Rodney Howell:

September of this year?

>> Harry Hannon:

Yes, sir, if I'm alive then. If not –

>> Rodney Howell:

I had to give you a little grief there. So we can – our – all of our agenda-ologists are right here, and – so that they will put you on the agenda for September to discuss the second sample, because I think we won't stop it. But Jane, thank you very much and so forth. Are there further comments that we'll –

>> Harry Hannon:

I didn't say we'd have a resolution or an answer; I said we'd have a report.

>> Rodney Howell:

But it will be detailed; I'm sure, after all these years. Any other comments?

>> :

I have a quick question. Jane, the figures you gave for tests that are mandatory at this point – I'm in Pennsylvania, and if I recall correctly, we've only had six mandatory tests, and they [inaudible] tests were not – to the point last year, not supposed to go into effect until July. And there's concern whether we'll be able to – when you have, like, 33 tests for Pennsylvania, and I don't think that's the current situation.

>> Bradford Therrell:

This is Brad, and that's the number that the State health department gives to us. They say they are mandated to do that. They will do it by July 1, and we should have it on there as their mandate.

>>:

Okay.

>> Rodney Howell:

Well, that'll be very interesting. And so –

>> :

The law says 6 months, 22 additional tests, right?

>> Bradford Therrell:

Yup.

>> Jane Getchell:

Yeah, I think that's a clarification that Brad made for me – was, what's mandated isn't necessarily what's done.

>> Bradford Therrell:

That's correct.

>> Jane Getchell:

And this is what's mandated.

>> Rodney Howell:

Thank you very much. Since – we're really quite on time and so forth, and it's time for a break, and I would – do not disconnect and so forth. Stay connected, and we will return promptly at 3 o'clock to hear a preliminary report on Krabbe disease. We're not going to vote on Krabbe disease; we're going to hear a preliminary report and have a chance to comment. Thank you very much. We'll return at 3.

[Break]

>> Rodney Howell:

I'm going to ask Dr. Puryear if she will again call the roll, because we're about ready to go hear a draft report on the Evidence Review Workgroup. Michele?

>> Michele Lloyd-Puryear:

So, Dr. Alexander? Dr. Boyle?

>> Coleen Boyle:

Here.

>> Michele Lloyd-Puryear:

Dr. Buckley?

>> Rebecca Buckley:

Here.

>> Michele Lloyd-Puryear:

Dr. Calonge?

>> Ned Calonge:

Here.

>> Michele Lloyd-Puryear:

Dr. Dougherty?

>> Denise Dougherty:

Here.

>> Michele Lloyd-Puryear:

Dr. Frempong?

>> Kwaku Ohene-Frempong:

Here.

>> Michele Lloyd-Puryear:

Dr. Kelm? Ms. Monaco?

>> Jana Monaco:

Here.

>> Michele Lloyd-Puryear:

Dr. Rinaldo?

>> Piero Rinaldo:

Here.

>> Michele Lloyd-Puryear:

Dr. Skeels? Dr. Trotter?

>> Tracy Trotter:

Here.

>> Michele Lloyd-Puryear:

Dr. van Dyck is – had to leave for a senate hearing. Dr. Vockley?

>> Gerard Vockley:

Here.

>> Michele Lloyd-Puryear:

So we are missing Dr. Skeels, Dr. Kelm, and Dr. Alexander, but we have a quorum.

>> Rodney Howell:

Thank you very much. We're going to now move on, and we're going to ask Alex Kemper to provide us with a review of a draft report on the Evidence Review Workgroup having to do with Krabbe disease. And again, let me remind you – is that this – we will not make votes on this today. This is a preliminary review for your comments and input before the final review, which will be presented for our final recommendations in September. Alex?

>> Alex Kemper:

Thank you very much, Dr. Howell and members of the committee. I'm happy to be able to update you with the work of the Evidence Review Workgroup as well as our focus today on Krabbe disease. So just to recap our recent progress and activities, the SCID report was revised, and the final draft was submitted in – back in April. In terms of Krabbe disease, the preliminary report has been submitted and is part of the meeting's virtual book. We'll be discussing that today. And we'll be revising the report based on the discussion today and additional review that we plan to undertake.

And again, I'd like to highlight what Dr. Howell said just a minute ago: that this is our preliminary work, which it certainly is. And as I go through, I'm going to identify some particular areas where we'd like to supplement what's in the current report.

I'd like to go ahead and thank our Workgroup members, including Alixandra Knapp, who's really key to pulling things together. And also, while my name is up there, I'd like to mention that although I'm at Duke University, where Krabbe work is being undertaken, I'm not affiliated with those groups. And I'm fortunate to have a very helpful team to make sure that we present all the available evidence in as fair a way as possible. And certainly the program director, Dr. Jim Perrin. That's very helpful. I'd like to also thank Dr. Browning, Dr. Comeau, Dr. Green, Dr. Lipstein, Dr. Prosser, and Denise Queally, a consumer from the PKU family coalition, for all their hard work on this.

So now, moving to Krabbe disease – as many of you know, it's due to a number of different gene mutations for the hydrolytic enzyme galactocerebrosidase or GALC, which – I'll refer to it during the rest of the presentation today. There's over 60 disease-causing mutations that have been identified in the GALC gene, leading to the four main clinical subtypes, which include early infantile Krabbe disease, which you'll sometimes in the report hear me refer to simply as infantile Krabbe disease. There's also a late infantile, a juvenile, and an adult-onset form of Krabbe disease. Because of our interest in newborn screening, we're going to be focusing on the early infantile Krabbe disease form, which is associated with extreme irritability, spasticity, and developmental delay before 6 months of age, leading to a decerebrate state in early infancy, with most children dying by 2 years of age.

So the rationale for the review is that without treatment, individuals with the early infantile Krabbe disease usually die by 2 years of age, as I just mentioned. Hematopoietic stem cell transplants or HSCT is listed here on the slide, before the onset of symptoms may decrease morbidity and mortality associated with infantile Krabbe disease. There are now methods to screen infants for Krabbe disease by measuring GALC activity in dried bloodspots. And most importantly, New York State began newborn screening for Krabbe disease in August of 2006.

So the materials that were included in your preliminary report today include detailed methods of the literature review, a summary of the evidence, tables highlighting key data from abstracted articles, tables of studies that were excluded due to having few subjects – and again, I'll be talking about this in a little bit – and a bibliography of all identified articles. This is – follows our traditional method for these reviews.

So we conducted a systematic literature review to summarize the evidence from published studies, and we also undertook an assessment of critical unpublished data from key investigators or other experts in the field. The specific topics that we reviewed – again, we focused on the early infantile form, where the incidents are prevalent; the natural history; testing, including the screening and methods of diagnosis; treatments; and identification of the critical information still needed – that is, identifying the gaps in the knowledge about Krabbe disease.

In terms of the systematic literature review, we looked at literature that was published between January of 1988 and March of 2009 in a variety of different datasets, including Medline, Ovid

In-Process, and other non-index citations database. This review is restricted to English language only and only includes human studies; that is, we did not look at animal studies. We excluded reviews, editorials, or other opinion pieces; case reports or case series of four or fewer subjects; studies that weren't focused on infantile-onset Krabbe disease; and studies not addressing one of the key questions that I mentioned just a minute ago. We also reviewed references from the nomination form and the bibliography of reviewed papers. And so we ended up with 322 abstracts, which we've – looked like they met our preliminary inclusion criteria, of which 75 were selected for in depth review, leading to 27 articles that met all inclusion criteria. And again, all of this is in the material that you were sent prior today – to today. In terms of the papers meeting the review criteria, it's not surprising that most of them were case series.

In terms of quality assessment, we did do quality assessment by study design and by study goal. So I have an example here of the kind of thing we did. I don't want to belabor the point, because this is exactly what we did previously with SCID. But for example, if you look at studies of sensitivity and specificity screening, there were three tiers: data obtained from screening programs in the United States population or similar; data from systematic studies other than whole population screenings; and then finally, the lower tier would be data estimated from the known biochemistry of the condition.

In terms of unpublished data, we contacted experts identified through our literature review discussion within the workgroup and recommendations by other experts. And we included experts from varying Krabbe disease domains, such as screening, treatment – and advocacy groups as well.

Now, on the next slide, on this slide here, you can see a list of experts that have been contacted thus far. And the ones that are in white are ones that provided data that are in the report that you have today. Some other experts were either unavailable or deferred to other people. This is one of the areas that I wanted to highlight – that we are going to focus. There's – there are other experts that we want to contact, and there's more unpublished data that we would like to include in the report. So this is certainly not the final list of experts that are going to be included in the report.

The next slide lists quality assessments of the natural history studies. There were eight studies looking at genotype-phenotype correlation or looking at incidence instead of looking at other factors related to the natural history of disease. And what I'd like to do is just move onto the next slide, which summarizes what we know about the incidence. So the incidence of Krabbe disease ranges between ½ and 1 ½ per 100,000 population, with most estimates being close to that 1 per 100,000 number.

In terms of the natural history, as I mentioned earlier, there are four main clinical subtypes that are distinguished by the age of symptom onset. Most children with early infantile Krabbe disease are diagnosed with extreme irritability, spasticity, and developmental delay before 6 months of age. Without specific treatment, children go into a decerebrate state in early infancy, with most dying before 2 years of age. There's – this is very important: There's poor genotype-phenotype correlation other than homozygosity of the specific 30-kilobyte deletion, which is strongly predictive of the early infantile Krabbe disease. And the low levels of GALC activity in and of

themselves do not entirely predict the age of symptom onset or the severity of the illness, including white matter changes in the brain.

So next I'd like to talk about the screening methods. So screening is available now through dried bloodspots, and it's a combination of enzyme assay – and followed by tandem mass spec to find the enzyme products. So it's not simply going directly to the tandem mass spec; there's this first step ahead of time with the enzyme assay.

Next I'd like to move into studies looking at test characteristics. You can see on this slide there are relatively few studies of the test characteristics. This slide here – which, on the little monitor that I'm looking at, is quite small, so hopefully you all can see it better – summarizes five of the major studies of the screening test. But instead of going through each of these individually – and again, this is available in your report – what I'd like to do is focus on the report of Duffner et al. from the New York State Screening Experience, which I think is really the most pertinent for our purposes today.

So what I'd like to do first is walk you through how the – how screening works in New York State for Krabbe disease. So at the top of the slide, you can see that there's screening done inside the scribes with the enzyme assay mass spectrometry. And there are three possible outcomes: If your screen is greater than 10 percent of the daily mean, then you're considered to be a screen negative. In contrast, if your screen is less than or equal to 8 percent of the daily mean, that's considered a positive screen. There's an indeterminate range; that is 8–10 percent of the activity. And if you fall into this group, then there's genotyping, and if you have at least one of the genotypes associated with the development of Krabbe disease, then you move on as if you tested positive; otherwise, you move to the left as screen negative.

The second-stage impulse position is family notification and a new blood sample that's obtained – and then that moves us down to the – to Stage 3, the second-tier laboratory testing, where the initial assay is repeated and confirmed. And if you still have a suspicious result at that level, then you move on to a child neurologist. And you're categorized into one of three groups: There's a low risk, moderate risk, and high risk based on how low your enzyme activity is. And then you proceed through diagnosis based on your risk stratification. And I'm going to talk about the process of diagnosis a little bit later, but I first want to just focus in on this slide here, which has the screening algorithm on it.

Now, what we've learned so far in talking to those that are in charge of the New York program is that they've screened about 727,000 newborns. Of these, there are 128 children who have screened positive and have completed the process of being referred to the child neurologist. What I'm unable to do at this point is show you exactly where these numbers exist on this chart – in other words, adding numbers to each particular box. And that's another one of those things that we need to add prior to finalization of this report. Now, of those 128, 36 were characterized as low risk, 11 as moderate risk, and 7 as high risk. And of those seven, two have been referred on for cord blood transplants. Again, I'm going to talk a little bit more about the diagnosis and treatments in a little bit. Again, as I was talking about, what we don't have so far is the – missing in terms of positive at each level in each little box. And also, I don't know – I can't provide you today information about loss to follow-up, so whether or not this 128 is perhaps a subset of other

children that have tested positive. And that's information that we'll be going back to gather for the next draft of the report.

This slide, however, just is another way of looking at the data that I just showed you. So again, there were 727,000 newborns – were screened; 128, or about 17.6 of 100,000, were referred for the diagnostic evaluation. There were seven high-risk newborns, two of which were referred for transplant. One of those was homozygous for the 30-kilobyte deletion, and the other was a compound heterozygote, which included the 30-kilobyte deletion as well as the novel mutation. There were 11 moderate-risk infants and 36, who were about 5 out of 100,000, low-risk newborns.

Now let's change gears a little bit, now that I've walked you through the process of screening, and talk a little bit about diagnosis. So there's been a consensus diagnostic rating scale that has been developed in New York State. And you essentially earn points for different findings, and when you hit a certain point on the scale, then you're referred for a transplant. Now, in terms of the process of diagnosis, if you fall into the high-risk group, in the first year of life, you're followed monthly with neurodiagnostic studies, including MRI, LP, and auditory and visual response and nerve conduction studies every 3 months. In the second year of life, you're followed for every 3 months with those neurodiagnostic studies happening semiannually. If you are in the moderate-risk group, in the first 2 years of life, you're followed every 3 months, but those neurodiagnostic studies are annually unless there's some finding on exams. And if you're in the low-risk group, you're followed in Years 1 and 2 every 6 months, and the neurodiagnostic studies are done only if the exam is abnormal.

So that's the process for treat– for diagnosis. Now we're going to talk a little bit about treatment. The treatment that's made available now to children who are diagnosed with Krabbe disease is a hematopoietic stem cell transplant, and the potential sources for this include bone marrow and umbilical cord blood. And a lot of what I'm going to be talking about for the New York program is actually from umbilical cord blood. One thing that I would like to highlight, since our last report was about SCID, is that unlike SCID, treatment for Krabbe disease does require preconditioning and therefore exposes the children to that potential risk.

So we found five studies looking at the effectiveness of treatment. And if you look in your meeting book, you'll see that what we've done is, we've taken these studies, and we've divided them up into those children within each study who were treated when they were asymptomatic or treated when they became symptomatic so that you can understand the benefits of early treatment. And of course, with the New York State algorithm, it's – these children are in the very early stages of becoming symptomatic, sort of on the cusp of becoming symptomatic versus the later symptomatic treatment. Instead of going through each of these studies, though, what I'd like to do is highlight the one that I think provides the most comprehensive data for our purposes today.

And I'm going to go back for a second. This is the study by Escolar. There were actually two publications, in 2005 and 2006. And the – I'm going to show you some graphs that illustrate things much better than I can say on the phone.

So these graphs look at treatment mortality between 1998 and 2004 and is based on 11 asymptomatic newborns and 14 symptomatic newborns that underwent UCT; that's umbilical cord transplant. And you can see that in this study, the – all the asymptomatic newborns survived the process of transplantation and – up until 72 months of life or so, which was the period following. The children who were treated after the development of symptoms, you can see, had a much greater risk of mortality in the first 36 months of life. And then the curve that falls off more precipitously is an untreated control group.

So from the New York State program, as I mentioned, there were two children that were referred for umbilical cord blood transplant. One of the two infants died from complications of transplantation, that being vasco inclusive disease and multisystem organ failure. But beyond mortality, we were interested in morbidity: What's the effect of treatment on other parameters of how these children are doing? And again, you'll see that we've listed the studies that we found that address this in particular, and we've divided them up into treatment during asymptomatic phase and treatment after children had already become symptomatic. And as I've been doing, I'd like to focus on one particular group of studies by Escolar again.

This slide shows a series of developmental outcomes. And if you look, there's a gray zone that shows the normal developmental track of a child, and the different colored lines represent individuals who were treated in the asymptomatic period, and then the dark lines towards the bottom are those children that were treated after the development of symptoms. And you can see across the top that there's cognitive development, adaptive, and so forth. Now, what I'd like to highlight is that among the early treated groups, there was concern that fine motor control interfered with cognitive function testing, although cognitive function testing in general seemed to show that these children were doing well. That – similarly, motor involvement affects expressive language; however, receptive language seemed to be going on track. Now, during the second and third year of life, there was progressive spasticity in the lower extremities and truncal weakness developed in two of the six children, and – these are children who were treated early – and two had severe delay in fine motor function. So it's a complicated story, and you can see that there are changes over time.

Now, I'd like to move now from treatment effects to the availability of treatments for Krabbe disease. Now, from our expert interviews, what we found is that Duke University and Minnesota have been the main sites for treating Krabbe disease with stem cell transplants. Mount Sinai Hospital in New York City has begun to perform transplants. And there are approximately eight centers in the United States currently experienced in transplantation of infants with Krabbe disease. Transplants performed for both early infantile- and late-onset Krabbe disease at sites besides Duke and Minnesota in the U.S. include Chicago, Nationwide Children's Hospital, St. Louis Hospital, and then Montreal, Vancouver, and then Devos Children's Hospital in Michigan, and there are two centers in Illinois.

Now let's consider issues related to evidence of cost-effectiveness. The experts that we spoke with identify costs associated with newborn screening in terms of the cost of setting up the program or the cost of the reagents, but there's really insufficient data available for complete economic evaluation.

So now I'd like to summarize the information that I've just presented. So the incidence of Krabbe disease is at least 1 in 100,000 newborns in the United States. The New York State data indicate a lower incidence; they found about .28 per 100,000 than initially estimated for early infantile-onset Krabbe disease. The New York case definition is based on a combination of laboratory and clinical findings, and this case definition for diagnosis requires frequent follow-up examination and testing over at least 2 years.

In terms of treatment, without treatment, early infantile Krabbe disease is a devastating illness. Cord blood transplant after the development of symptoms does not lead to meaningful neurologic improvement. Stem cell transplant carries some risk of mortality. And after early treatment, cognitive development may be normal, but some children may have persistent fine motor delay, and some children may develop gross motor function delay. And there are no long-term outcome data after early childhood and beyond the period of time that I showed you in those previous slides by Escolar et al.

So in terms of critical evidence that's still needed, we identified issues related to test accuracy, so there's limited data regarding the sensitivity and specificity of screening, and we hope to fill that in a little bit more before our next report. The Early New York Experience underscores the challenge of establishing whether or not a child requires treatment. And there's no data out there regarding the accuracy of other screening or diagnosis methods in large populations.

In terms of feasibility, New York's experience suggests that screening is feasible. Illinois has mandated newborn screening for five lysosomal storage diseases, including Krabbe, which is projected to begin some time in 2010. And there's no data regarding the ability of other newborn screening programs to offer Krabbe disease screening.

In terms of the acceptability, there's no systematically collected data regarding consumer attitudes towards Krabbe disease. And the current strategy for diagnosis may impose harm to families and children related to frequent follow-up, uncertainty, invasive testing – that sort of thing.

In terms of the value or harm of early treatment, treatment may prolong survival and significantly improve developmental outcomes. But the current evidence is limited, especially regarding the risk of stem cell transplants and the long-term developmental outcomes.

In terms of cost-effectiveness of both screening and treatment, as I pointed out before, there's just not sufficient data for us to model these things.

And then, in terms of the adequacy of available treatment centers, there's no data out there regarding the variation in treatments and outcomes and the capacity to provide such care. Future data from the registry of Pediatric Blood and Marrow Transplantation Consortium, the PMBTC, may provide evidence for treatment availability and variation, which would help fill in some of these gaps.

So I'd like to conclude there and, I guess, pass the baton back to Dr. Howell. Thank you very much.

>> Rodney Howell:

Thank you very much, Alex. And we have asked that Dr. Piero Rinaldo, who's a member of the committee, walk us through his comments about this presentation. Piero?

>> Piero Rinaldo:

Slides? Okay.

>> Rodney Howell:

Yeah, I think your slides have appeared.

>> Piero Rinaldo:

As we have done in the past, I think we go through sort of a first read of a draft report – and I think it's important to underscore the point made by Alex that this is still work in progress – by a member of a committee, and I've been asked to do this. I just show you three quick slides that repeat some of the same things said by Alex. These are points taken straight out of a nomination form. Again, there are the three basic categories: the condition, the test, and the treatment. And again, there are here the information about – I think there's no doubt about the severity of the natural history of Krabbe disease, certainly in the early infantile form that leads to death. In terms of the test, this is certainly a change from discussions we had so far, because clearly we have the experience in New York that, according to the report, now has data as of April of this year on 727,000 babies. So clearly, we have here – type of evidence that we haven't encountered yet for the other conditions that have been considered. And once again, it's basically based on enzyme product assay or reaction product assay with – combined with tandem mass spectrometry and a second-tier test confirmation based on full gene sequencing.

Next slide – well, it's a treatment. Again, you heard from Alex, and this is again our concept taken from the nomination form. And clearly the issue here was the representation of efficacy as really that the transplant could lead to normal cognitive development, whether there already was early recognition of some risk. The survival seems to vary from center to center, but nevertheless, there is, I think, answers that possibly – you know, death is certainly a possible outcome after the transplant.

This is not readable, but this is just a one-pager summary. As you know, once nomination has cleared – technically, just in terms of timeline, the nomination was submitted in November of 2007; the administrative review was completed in January of 2008. And you can actually – perhaps you can see – I can use this feature, but up here – sorry, a little more – there is – says that the period of review by a subgroup of the committee was between February 20 and was completed in March of 2008.

To summarize the conclusion, the overall recommendation is highlighted here. And the group stated this disorder – the recommendation that came forward to the full advisory committee – and I believe it was voted to proceed with the Evidence Review Group – was that Krabbe disease

meets the criteria for evidence-based review, but there was already sort of early, you know, sign of what really – were the critical issues and [inaudible] the clarification of making sure that the system in place would identify those infants most likely to benefit from treatment and the efficacy of treatment.

This is a table that actually I prepared some time ago, but I thought it was worth including here. I'm really trying to summarize the – sort of the characteristic of the available evidence for Krabbe disease, but also other conditions – not all, but other conditions being really through this process. And you can see this is, again, a comparison between Pompe disease, Krabbe, and Fabry disease. And as you remember, Fabry disease was actually not sent for evidence review. And the point worth making – I'm sorry; wrong bottom – is that clearly, Krabbe stands up as a disease where we probably have the type of evidence that the analytical lab for population-based assessment was not found for the other conditions. On the other hand, there was – as you can see, the highlighted boxes – this issue if the screening is truly capable to identify cases most likely to benefit from treatment and also the availability of the defined treatment, where – I think, you know, somebody would deem to be still to be determined.

I presume that everybody, certainly in the committee, because of extensive discussion – probably people on the line are familiar with the analytic framework put together under the leadership of Ned Calonge. And this is really a mechanism to systematically ask the critical questions that lead to the evaluation of the evidence and eventually to recommendations. And the first question is the one that we discussed extensively about SCID, and it's about the existence of direct evidence that screening for the condition at birth may lead to improved outcomes. And of course, the current definition of the direct evidence is something will only arise from randomized control trials, and that obviously is not available at this time. And as you probably remember, we had a sensitive discussion on really the rationale for asking a question that almost always will lead to a negative answer. On the other hand, I think Ned has been quite effective in really evolving the concept of direct evidence and say that it can certainly be, if not replaced – but complemented by what he called the chain of evidence, where you really systematically review the evidence about analytical validity, clinical validity, and clinical utility and also that, really, recommendations in the end should be based on the certainty of that benefit, and I'll talk more about that.

The second question comes and is about the case definition. In other words, can we really clearly define what constitutes a case? And this is where, as of the draft report underscores, we're obviously relying on a single source. And my read of the material available to us – that we really are now following the case definition of New York State and is a definition that is specific for the cases with high risk of early infantile onset. And there are three elements: the galactocerebrosidase activity in WBC less than .15 nmol/h/mg protein, keeping in mind that abnormal results are considered anything less than .5. As Alex has mentioned, the only evidence of genotype-phenotype correlation counts from the presence of this 30-kb deletion. Again, we have learned so far that one patient detected in New York was monozygote; the whether the other had one allele with this deletion; the other was one still being investigated – of course, the clinical evidence of early signs of neurological disease.

Now, the third question is about the screening test: Is there a screening test? And you've already seen this graph that is included in the evidence report that was shown by Alex earlier. And I just

add a few comments based on my read of material available. There seems to be some areas that perhaps could be clarified in greater detail. I read in the report that there is actually another sort of subgroup here, and that is that if the results are below the 20 percent of the daily mean, there will be at least a retesting. So I think it would be useful to know not only the – really the – how the algorithm worked – would work in those cases, but also really get a sense of the traffic: How many cases? I'm still wondering if there is a defined and sort of convincing need of having this moving target, if you want, of basing results on the daily mean rather than some absolute values. And that's also, I mean, an element of the evidence that would be interesting to know. In other words, it makes me nervous that a certain – the same absolute value could mean normal one day and perhaps abnormal on another.

The other point that is perhaps in need of some clarification would be that – when exactly the molecular testing. Now, you see, my calculation of how many cases received went to full gene sequencing is based on a comment that I found in the draft report that overall, 220 cases were sequenced. So as we know that 128 cases in the end were deemed abnormal, it would certainly be very informative for the committee to know what exactly was the outcome on the remaining – there's almost 100 cases that – apparently, although they were sequenced– I'm assuming that the sequencing happened at this level, but there seems to be another 100 cases that – they didn't go through; they didn't move to Stage 2. The question is, were they carriers, or were no mutations found? I think it would certainly give us greater insight on the effectiveness of the primary screening of a Stage 1.

As Alex has mentioned earlier, I'm now going to revisit the fact in the end, we are dividing patients where – the normal result in these three groups based on the level of residual activity. Now, the clinical validity is somewhat – we can extrapolate from this data. And the first line is one where we can tell that of 128 cases that were deemed abnormal, at least 74 were false positives. In other words, they were not considered to belong to any of the risk categories. If we go in a little more granular level, we – you already heard about the two patients who were referred for transplant. And then there were actually – not all; there were five additional patients that seemed to meet the case definition of high risk – nevertheless were not referred. Then there were 11 cases with moderate risk and 36 with a low risk. So these are the same number we have seen before. Now, it's interesting, because we can extrapolate, assuming that each of those group would actually represent an estimate of the incidence of the disease or the detection rate of the disease. It seems that, you know, we're really looking at a pretty broad range. Clearly, if only 2 of those 128 patients turn out to be really two cases of early infantile Krabbe disease, that will actually make the incidence of the disease somewhat less common – that clinical – based on – what is the estimate based on clinical ascertainment. You see, if you look at the high risk of 7 cases – indeed end up pretty much – all right; let me go back – only a hundred – 1 in 100,000. The point I really would like to make is that it is unlikely that all these cases are real, because if that were the case, we would have an incidence around 1 in 13,000, almost an order of magnitude higher of what has been established by clinical ascertainment. So my estimate is that it's likely that a fair number of these patients in the blue rectangle, certainly in the low-risk and possibly in the moderate-risk group, will turn out to be the equivalent of false positive cases, meaning the patient will not require an intervention. So in the end, I think it's probably likely that the existing estimates will turn out to be fairly accurate to be a disease of 1 in 100,000 births.

Now, I have to say that the system implemented by New York State seems to work in terms of specificity remarkably well. In fact, you can see that it doesn't really matter, of this group of patients, how many will turn out to be false positive, because [inaudible] we have a false positive rate that is around .01, .02 percent. So in the end, it is likely that this system will certainly pass with flying colors the assessment of specificity, because there is very little noise using the two-tier system. It's somewhat a different story when we look at the positive predictor value, because, you know, it's – you can see that depending on what group you consider, you can see values anywhere between 2 and 42 percent. My – again, based on what I've seen so far, I think it will turn out to be somewhere in the ballpark between 5 and 15 percent. And again, it's a more benefactable performance when we strictly look at the – you know, how to evaluate the outcome of the screening.

Now, you heard from Alex the assessment of benefits. I don't really want to go in that level of detail, but clearly, we have the option of a stem cell transplant, which is – very importantly, when it comes to the need of justification for screening that is really especially for the early infantile form – seems to be a narrow window – is not as, well, similar to what we have heard when we discussed [inaudible] really the first month of life. The benefits, of course, include improved survival, improved neurological status, and a slower progression of disease. I just took some of the data from the report. I think that the number in the group of cases detected by screening being – the denominator is so low, you know, and having already one fatal outcome out of those two, I don't think it's completely fair. I think that the data from the literature clearly show that transplant in patients who are still asymptomatic – again, the population – one of the group that we're – I've described in the literature – out of 11 patients with positive family history, 5 actually benefited from prenatal diagnosis. It's – I think that there is – it's likely that they – which we need to see the evidence that transplantation in asymptomatic patients will actually have better survival; locations will actually reach that point when already symptomatic – but I think we need better data, more data.

I think that the report summarizes very well the concept of benefit. This is taken word by word out of a draft report, and I just want to read it. The transplant appeared to benefit disease, but over time, most children have developed and, you can see, slowly progressed in specificity, somatic oral failure, expressive language deficit, and poor brain growth. And the conclusion – the summary of the evidence in the report is that it is unclear whether transplantation significantly lengthened survival.

There is the other side, especially when you go to the concept of a net benefit, which is benefits minus harms. And I think that this is probably going to be a critical point in our discussion and in whatever recommendation will come out of this process, because there clearly are – there are recognizable harms. There seems to be the – certainly a possibility of false positive results, although, again, I have to say that this is very low. Nevertheless, I think there is a relative weight on the fact that the families with false positive results will – it's unlikely they will have a quick process and a quick resolution, so this can drag for quite some times, as you have heard of the current follow-up protocols. And so this – although the number is likely to be quite small, the impact of these individual families could be quite substantial.

The concept of detectional carriers – again, the sequencing of the full-allele gene should somewhat help minimize this, but we obviously need to see the data. There is this huge issue of uncertainty of clinical outcome in cases of moderate and low risk. These patients, at least early, will go through a pretty aggressive follow-up. And I think what is critical to have is somewhat a definition of endpoint of – I'm certainly concerned about the appearance of an open-ended follow-up, and I think it would be important to be clear when this follow-up should somewhat be discontinued.

As I mentioned before, there is certainly a component of family stress and even hostility. I'm quoting from the report that the word used to describe the feelings of one of the families is that they were "furious," and so I don't think that the group – Evidence Review Group used that word lightly. There is a real risk of mortality post-transplant, and again, the data of one of the first two has clearly shown that this is the case. And I think there seems to be, you know, a bubbling controversy, perhaps [inaudible], but I don't think it, you know, will take a long time before the public or the families who are receiving counseling will become aware of the fact that the specialists – the providers of care don't seem to really be in sync at this time; there seems to be a brewing controversy, and I think that could be quite detrimental overall to the whole process.

Finally, the six critical questions – the key question is about cost-effectiveness. And Alex has mentioned – is not available at this time.

So in summary, I say there are five points worth mentioning when it comes to gaps existing at this time in the available evidence. The testing algorithm may need revision(s), but certainly we'll need some clarifications that will cover all the actions taken – for example, get a sense of magnitude of those retesting who are less than 20 percent – getting a better idea of what happened, what was the outcome overall of 220 patients who were sequenced. The case definition is unresolved, especially when it comes to the moderate and low risk. The benefits of a transplant are uncertain at this time. There seems to be, again, differences in opinion. I think there is little doubt that substantial harm is possible. And again, cost-effectiveness is undetermined.

So this slide I think I copied from material presented by Ned Calonge, but it's – a critical point is that translating evidence and/or lack of into recommendation needs to rely on the judgment: judgment of the magnitude of net benefits, judgment of the adequacy of evidence, and the judgment of the certainty of net benefit. So at this point, these are the four possible recommendations that are in sort of the arsenal of advisory committee. And I just want to make a point that – I just want to say that this time – and not much – if we just, you know, even put aside the evidence [inaudible] our recent, quite active history and evaluation of our – I think if Pompe disease – SCID were not deemed ready [inaudible], my personal opinion – and certainly, people are more than free to disagree – is that if those two conditions were not ready for addition to the core panel, I personally believe that Krabbe disease – which one of the other recommendation, I think, will take some more discussion. And that's all I have.

>> Rodney Howell:

Thank you very much, Piero. Let's open up the discussion for the committee. Are there questions and comments for Alex and/or Piero?

>> Ned Calonge:

Rodney, this is Ned. So just a couple of things real quickly: I think Piero actually answered the question, but I've spent a lot of time wondering how the asymptomatic kids were detected for the Escolar study. And I think knowing that helps us kind of understand whether or not those would be children picked up by screening. So that's always an important question: Are the kids in the treatment trial the same ones that would be picked up by screening? And similarly, why weren't the asymptomatic kids picked up and others?

So that's one issue. The second issue is whether or not there's any way to help answer Piero's diagnosis question. The natural history uses the word "most" very often, and so I'm unclear at what point you would no longer be early infantile. And so, I think trying to pin – if there's any way – maybe there's insufficient evidence, but giving a better sense about how long you have to wait before you say, you know, you're not going to be early infantile Krabbe, I think, is important.

And then, I think the last issue, other than to say I agree with Piero's preliminary assessment for the full reviews and – but when there's, like, a key article like the Escolar paper on treatment, sometimes, Alex or Michele, it's useful to distribute a PDF of that, if possible, to the committee members so that we're basing our review on not only the excellent review that we've been provided but – are able to look at, you know, somewhere between one and three key articles ourselves.

>> Michele Lloyd-Puryear:

Okay. We can do that. That's a good idea.

>> Rodney Howell:

Very good idea. And there's a publication coming out from Duffner that summarizes –

>> Michele Lloyd-Puryear:

Yes, the committee has that.

>> Rodney Howell:

Yeah, [inaudible] after that. Any further comments or questions?

>> Rebecca Buckley:

Yeah, Rodney, I have a question. I'm sorry; this is Rebecca Buckley. The five who were not referred for bone marrow transplantation – do you know why they were not referred, Alex? Or –

>> Alex Kemper:

All I can tell you is that they haven't developed the physical exam findings concerning – for, you know, the very beginning of symptoms. But that's something that I want to revisit again and find out exactly what's going on with those five children.

>> Rebecca Buckley:

I thought that the advantage of doing it before they develop any symptoms was what they were

>> Alex Kemper:

Well, yeah, there's probably – it's – yeah, I mean, it's – once you are stratified into risk category, then there's that complicated follow-back rhythm and scoring system that includes both physical exam findings as well as nerve conduction and MRI findings. So it's really – it's not like they're completely asymptomatic, but they're, like, just on the – you know, just touching symptomatology.

>> :

And Alex, this is a quick question: The one child that died – it wasn't the child who was homozygous for the KB mutation?

>> Alex Kemper:

You know, I'm not sure; I have to go back and check.

>> James Perrin:

Alex, this is Jim Perrin. Just a comment on the five high-risk non-transplant group: I think we gathered some information from Dr. Escolar about the early findings on MRI and others of children that she has been following. And my understanding is that the New York sample of five is not demonstrating any of those changes. Is that what we understand?

>> Alex Kemper:

I have to go back and look, but –

>> Rodney Howell:

And I think it would be very important to clarify that for the committee when we see the final results and so forth.

>> Michael Skeels:

This is Mike Skeels. I've got a question for either Alex or Piero. I understand that a real cost-benefit analysis hasn't been done, but has New York made even an estimate of the cost per true positive found?

>> Alex Kemper:

So the cost is – that we have is related to just the cost of the equipment and the cost of the reagents and whatnot that you need for the – to do it, but I have not seen or asked them about specifically the cost per case detected or the cost per positive found. But again, one of the things that I have to go back and do is revisit that whole screening algorithm with New York to make sure that we have the numbers in each box before we even go and, you know, add the cost numbers into there.

>> Rodney Howell:

They should be able to provide that accurate data, because it's done in a very distinct laboratory with distinct personnel and equipment, so they should be able – as far as the whole testing part of it, they should be able to provide you very accurate data.

>> Gerard Vockley:

This is Jerry Vockley. I think the New York experience and reporting of their data is – I think they – absolutely crucial here. You know, in the recent doctor publication, the pediatric neurology one from that just – was just out this year, it is essentially impossible to tell from that how many babies were in each stage. You know, I mean, they – at the publication time, it was 550,000 babies, but I have absolutely no idea how many babies fall into less than 8 percent activity, 8–10 percent activity, or just get called screen negative. And what bothers me is that it didn't look like Alex and his group were able to get that data, at least for this draft. I would suggest that, minus the data, there's is no way we can act on this. So I think that's going to be critical.

>> Rodney Howell:

Alex, did you actually interview the folks in the New York State laboratory and physically visit them, or did you just ask them to fill out a form?

>> Alex Kemper:

They believe in – Jim, correct me if I'm wrong – they did theirs on – they filled out a paper form. I need to – and again, there's a very – because of the timing and the preparation of this preliminary report, there wasn't very much time to spend with them going over it. So that's – I don't want to leave the impression that the folk that are running the New York program are somehow not providing us the right data. I think that I may have been inarticulate in the way that I went about getting those numbers. So I'm – I feel that I'll be able to provide those numbers. But Dr. Vockley, I agree with you that we really need to have those numbers in each box in the full diagram.

>> Gerard Vockley:

They certainly didn't include it in their publication, which I would've viewed as problematic on review of the manuscript, but I wasn't asked to do that. So I'm putting my two cents here.

The other thing that bothers me – and Alex, if you – on page 22 of your draft report, it's the third paragraph; it starts with "Dr. Duffner reported…." Please read that carefully, because that seems to me to be an extraordinarily devastating description of the patients that we seem to be trying to identify. And if there's – it seems a little out of sync with maybe some of the results that Dr. Escolar is reporting. And it would be helpful to get a real sense of whether there is consensus in the field as to whether or not the cord stem cell transplant is simply attenuating disease and – but with a still fairly devastating outcome long-term, as would appear from that statement abstracted from this meeting – or that they actually may have a little bit of neurologic sequelae but are cognitively normal. I'm just not sure, based on the evidence as it's put forth here, which of those scenarios is the right case. So I mean, I know this is all preliminary, but please, if the committee could take a very, very close look at that, I think the language in describing the outcome of early treated and/or pre-systematic treatment is going to be critical for us to understand how to proceed here.

>> Alex Kemper:

Yeah, I agree, and that's an important hole that we need to fill in.

>> Rodney Howell:

And I think it would be very important to interview these people to get accurate data for that exact question rather than depend purely on a written document.

>> James Perrin:

So Jerry, this is Jim Perrin again. You're commenting on the paragraph that starts with "Dr. Escolar is following 17 patients…." Is that correct?

>> Gerard Vockley:

Actually, the one before that is the one that bothers me.

>> Piero Rinaldo:

I – like Jerry, I was quite impressed in a negative way by that statement.

>> Gerard Vockley:

Yeah, and that seems to be pretty damming, and I – if I were to see only that, I would – I think we would be – we'd have a hard time moving forward on this. And so, if that's the case, then we really want to be sure that that is an accurate description, or if there's some update on it that

would be – that would make us – make it seem a little bit more positive than what that paragraph – the way I read that paragraph.

>> Christopher Kus:

This is Chris Kus. I think that the idea is to figure out what information Dr. Duffner is using to make that statement, given that there's only, you know, one patient in New York State, and then when you read Dr. Escolar's next paragraph, they don't seem to match very well.

>> Gerard Vockley:

Yeah.

>> James Perrin:

So this is Jim Perrin again. We did talk in detail in an interview with Dr. Escolar. It was not from written statements with her, and it was actually where this paragraph comes from – the next one, the "17 patients report." And as I think Alex said, her most recent publication about these patients was, I believe, 2006, so she has not published this more recent data. But it – I think Dr. Duffner was really commenting on her perception of what has happened with Dr. Escolar's patients in general situation. And as you can see, the 17 children – there is, in Dr. Escolar's view, substantial difficulties with respect to their motor development. There is less question to the degree about their cognitive impairment, but more about their motor development.

>> Christopher Kus:

But – this is Chris – given that they don't match in terms of the discussion about expressive language and – relates to cognition that – Duffner's statement versus Escolar.

>> Alex Kemper:

Yeah, I think that – I mean, what we need to do is provide actual data there and not summary comments from their impression.

>> Rodney Howell:

I agree, and I think the other thing that concerns me is that you frequently quote people about – who report on observations of which they're not a part at all.

>> :

Exactly right.

>> Rodney Howell:

And that, I think, is just truly flat-out unacceptable, like you've got to call that out.

>> Piero Rinaldo:

And if I can add one more thing, I just realized that I really would like to know how the choice of those levels, you know, that define the low-moderate-to-high risk – how they reach – maybe that is in the literature, but, you know, how we know that .15 is what really lead to the case definition of a high risk for early infantile onset.

>> Alex Kemper:

Yeah, I mean, my understanding is, that was purely a consensus position, so –

>> :

My impression, too.

>> Piero Rinaldo:

Okay, but that – then at least they should provide the data – in other words, the individual data. So, you know, think of disease ranges if you want. I mean, what – I would like to know what is the normal population and what is the level seen in patients with Krabbe disease, so are they all 0 or – you know, there is some variability. So I think that – again, I'm sure that this – there is many – much more information behind the algorithm. I think it should be full disclosure of it.

>> Rodney Howell:

There's certainly considerable data about the absolute levels of enzyme that are seen in clinically diagnosed cases of Krabbe disease. I think the problem that's going to trouble us is that this is not population-based data, and it's going to take – it's going to be very difficult to decide what very low activity means. I mean, is this a new situation that we've not seen until we've screened the population? That would be a very complicated problem to do.

>> Kwaku Ohene-Frempong:

I have a question related to transplants. This is Frempong. In much of what I have read, it makes it sound as if every patient will get a donor, and they don't describe the transplants' conditions. Are these matched donor transplants, and if so, is the expectation that only about 25 percent of them will have their sibling match or unrelated donor?

>>:

I think they're cord.

>> Rodney Howell:

They're cord blood.

>> Kwaku Ohene-Frempong:

Cord – you still have to do some – I mean, cord is not always completely unrelated and unmatched.

>> Alex Kemper:

So, you know, those details are available at least in the – you know, the publications by Escolar and the ones that she's following out. I just didn't abstract that level of detail.

>> Kwaku Ohene-Frempong:

Because, I mean, it's very significant. I mean, cord blood can have an unrelated match, which is, you know, quite good, but it's not that any cord blood can be transplanted to any child without matching.

>> Gerard Vockley:

Jerry Vockley again. I think the other issue regarding transplants that I wasn't clear about in reading the draft – and I didn't go back and read the Escolar paper but will do so – it wasn't clear to me when you really have to do the transplant. So there's some – there's the information continuing after that that – of the section we were just on, talking – interviewing Barbara Burton about a couple of her patients who were both transplanted, but one was transplanted, I think, at a month of age or three months of age – at any rate, very early – and still developed symptoms. And so, the fundamental question that has to be asked: How early do you have to do this transplant? There was even some discussion about delivering babies early so that you could catch them before neurologic impact of the disease. And so, are we technologically able to meet this kind of need for extraordinarily rapid turnaround? You know, we're used to this in the context of the – some of the organic acidemias and the [inaudible] observation defects, where we know we've got to move fast to follow up. There, it's pretty straightforward. Here, I'm not clear yet about how – from the first hint of an abnormal, so the very first screen, 'til you assign a child to a risk group – what that time frame is. So again, if we can have a little bit more detail from the New York group, it would probably help a great deal in thinking about the feasibility of this.

>> Alex Kemper:

Yeah, I'm probably not going to be able to directly answer that question, but I can tell you that Dr. Escolar is working on that, because she mentioned on our phone interview that there's early white matter changes that you can actually see as early as birth. And I'm in the process of going back and looking at those papers to see whether they're really there. But she's working on new sensitive neuroradiology tests to identify who actually has neurologic findings at birth to sort of move the clock back. And she's interested in the very question that you ask, in terms of how early does the transplant have to occur to minimize some of these effects that we talked about.

>> Gerard Vockley:

I also need – we also need the – the flip side of that is, how quickly do we get data? In New York State, is it clear how – from that – from – what's the average age at the time of assignment to the highest-risk group?

>> Alex Kemper:

Okay, so just literally, how long does it take them to –

>> Gerard Vockley:

Yup. How long does it take before you can decide – you have to decide on a transplant?

>> Alex Kemper:

Okay, that's a good question that hadn't occurred to me.

>> Alex Kemper:

Okay, so I'll – we'll ask them about those timeline issues.

>> Rodney Howell:

Yeah, that data they presented – and I don't remember what it is and so forth. Now, Barbara Burton, who is a liaison to this committee – Barbara, you're on the phone, aren't you? Because it – would you like to make some comments?

>> Barbara Burton:

Well, the only thinking I'd make related to that last discussion is, it would probably be helpful to see if there's any guidance in the literature on the variability of time of onset of symptoms, even in the early infantile patient, because I think we're going to find that there's a spectrum of severity – age of onset on in that group, just as there is in many other diseases. And if we had a sense of the symptoms already in the first month of life, like the patient of mine that Jerry was alluding to, we might get a feeling for what fraction of those early infantile patients are not likely to benefit, because it's just not feasible to get them to the transplant in time.

>> Alex Kemper:

Okay. That's a good idea.

>> Jana Monaco:

This is Jana. I had a question and a comment, and this might be for you, Piero: Why is detection of the carrier considered a harm? [Pause]

>> Rodney Howell:

Piero, are you there?

>> Piero Rinaldo:

I am. It was actually a quote from the nomination form.

>> Jana Monaco:

Oh, okay.

>> Piero Rinaldo:

And so, I was a reporter in that. And I guess they – I don't see really how substantial harm could occur unless discrepancies – in other words, that's a situation that is not uncommon in a clinical context of patients who, you know, have a discrepancy. So let's say, "What if you have a residual activity very low, below the threshold, and you only find one mutation?" And I think it's not uncommon in certainly many conditions where people say, "I have a patient that biochemically is telling me something, but I cannot confirm it at the molecular level." So that, I think, could be a potential source of certainty, of sort of other –

>> Alex Kemper:

I think the issue is – there are two probable answers to that. One is that you could honest-to-goodness make a mistake. So, you know, if you didn't – if you thought you were identifying a carrier and it wasn't, then it – you've made a mistake one way, or you went the other way: you just transplanted the patient that didn't need it. I think more of the issue in that setting is the ongoing concern about the psychological aspects of being screened positive and then maybe a little bit of uncertainty at the end of it, if there's any clinical relevance to the finding of being a carrier. So it's probably less medical and more psychological issues involved in that setting.

>> Jana Monaco:

Okay.

>> Rodney Howell:

I think one of the reasons that they've made a big effort to do some diagnostic studies is to ensure that the patients have some evidence of the disease. And again, Hugo Moser has published earlier the value of peripheral nerve studies in the adaptive therapy and selection of patients with Krabbe, and I would assume that they, you know, [inaudible]. Are there additional questions that we would like the Evidence Review Group and so forth – I would like – personally, I have a few other things – we're relying very heavily on these very diseases on expert opinion, as you know, because we don't have controlled studies, and I would like the Evidence Review Group to explain how they select experts, because they – if we're going to use expert opinion, we ought to have some objective and consistent criteria for selecting experts. And that can clearly be done. Are there other questions or comments?

>> Coleen Boyle:

This is Coleen. I've been [inaudible] to see whether I'd ask the question or come up, and that is the issue of the case definition from the Escolar study. And on page 19 of the evidence-based review, having not read the Escolar study either, the report says that – state that a case definition used to diagnose Krabbe disease was not provided in the report. And I guess I'm just wondering and trying to evaluate the relevance of that study. Clearly, there is relevance; I'm not trying to understate that. But relative to the New York experiences in the cases that are being identified or considered cases there, it would be nice to go into some – and more detail just to make sure we're comparing apples to oranges.

>> Rodney Howell:

I was thinking along a similar line that it would be very interesting if the dried bloodspots are available from Escolar's patients to submit them to the New York screening program.

>> Coleen Boyle:

I think that's a great idea.

>> Rodney Howell:

But that would really, I think, be informative, because they are all set up, and they can do the enzyme assay readily, and they could do sequencing as necessary. And that would be a very nice comparison, which is probably – clearly not available.

>> :

Let's assume that the enzymes are stable in stored dried bloodspots.

>> Rodney Howell:

Yes, we're assuming that. But on the other hand, if it's unstable, we could at least sequence if worse comes to worse.

>> :

Yeah, well, I guess you could go to DNA.

>> Rodney Howell:

Of course; that's right. The other – thank you very much, Alex, for this very nice report. And if there's not any additional things, what we will expect to have is that you will continue to polish out and, I think, to continue to knock on the doors from the people who were, quote, "too busy" in your initial report and maybe urge them to get a little less busy and work with you to fill out

the forms and so forth. Now that the – all the grants that have been submitted looking for additional Federal funds, which apparently was what everybody was doing – and so forth.

Are there further comments about the Krabbe? [Pause] We will come back to that, and we will come back with additional information and discuss that when we meet in September.

>> Gerard Vockley:

Rod, what – this is Jerry Vockley again. What is the policy or maybe sense of the committee of actually bringing people to us for direct – I guess you call it "testimony"; I don't know. I mean, it's relying on the Evidence Review Group makes it – it does always remove it one step from us, and so, rather than us asking them, it may well be that for each of these reports, the Evidence Group that – could identify one or two key people who should present to the whole group. Or alternately, we could take a quick pre-read of the next draft and say, "Well, can't we have this person or these two people come talk to us?" I don't know if that's – if that fits within the time frame of a short meeting.

>> Michele Lloyd-Puryear:

This is Michele. I think what you – we can do that. And I think it's the latter, because I think the committee needs to identify what experts they would like to hear from more directly. But they need to be, I think, coming to the meeting and then not being there for the committee discussions. I mean, I would want to cut off – to remove them from that.

>> Rodney Howell:

Oh, yeah, I agree. And I would be strongly opposed to someone coming who has an opinion. But I would be strongly supportive of people who have experience and can share information about the test performance – how they did what [inaudible] very specific, direct, objective material that we might want to hear.

>> Michele Lloyd-Puryear:

But I think it has to be the committee, I think, identifying, based on the first preliminary draft, what experts you need to hear from. And to refine some of the questions, I think, would be really important. It just can't be a free-for-all where you have every expert and every self-identified expert.

>> Rodney Howell:

And the Evidence Review Group is going to do an excellent job of getting the evidence together, but if there is a single person or something that would really add greatly to the [inaudible] –

>> Michele Lloyd-Puryear:

And we did this with SCID; remember?

>> Rodney Howell:

Yeah. We clearly can do it, and so we can continue to discuss that. That's a good suggestion, Jerry. Thank you.

I think we're to the point of public comments at this point. And I only have one person on my list for public comments, and this is Jackie Wagner, who is the CEO, executive director of the Hunter's Hope Foundation in Buffalo. Jackie, are you there?

Good. Jackie, are you there?

>> Jackie Wagner:

Hello?

>> Rodney Howell:

Hi, Jackie.

>> Rodney Howell:

We can hear you well; thank you.

>> Jackie Wagner:

Well, I did not submit written comments. I was going to, and then I changed my mind because of the long list of comments that was submitted to the evidence review of testimonies in favor, of course, of adding Krabbe to the recommended panel. So if I might just say one word or two – how much I appreciate the hard work of all of you and the Evidence Review Group. And we are so looking forward to the further development and the research findings for Krabbe, and we'll just continue to pray and hope that one day, we will be able to identify every child with Krabbe disease, and we will be able to treat them. So thank you so much, all of you.

>> Rodney Howell:

Thank you, Jackie. On behalf of the committee, let me thank you and the folks who are with you who work on behalf of newborn screening. Although your focus has been Hunter's Hope, you've obviously expanded interest and have been extremely helpful in trying to bring resources to newborn screening broadly. We appreciate that.

>> Jackie Wagner:

Thank you.

>> Rodney Howell:

We're done. Is there any other comments? I think, ladies and gentlemen, we are done, and let me –

Oh, we have the calendar.

>> Michele Lloyd-Puryear:

Oh, yes. So if Rod's not going to say it, this is Michele. Let me remind you to get your calendars in so we can establish the 2010 meetings very quickly. So I think you have them from Carrie?

>> Rodney Howell:

Yes. And then –

>> Michele Lloyd-Puryear:

And if we could have them by the end of the month?

>> Rodney Howell:

Yep. And let me remind you that the next meeting will be September the 24th and the 25th, and it's at Marriott Pooks Hill here in Bethesda, and there'll be a face-to-face meeting, and we look forward to seeing you all at that time.

Any other issues or comments? Thank you very much for a very efficient meeting. And we're done.