SECRETARY'S ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

- - -

Thursday, January 27, 2011

Renaissance Dupont Circle Hotel

1143 New Hampshire Avenue, N.W.

Washington, D.C.

AFTERNOON SESSION

(1:10 p.m.)

CHAIRPERSON HOWELL: Before we start, I'm going to ask Michele if she will take the roll to see who's on the phone.

DR. LLOYD-PURYEAR: Dr. Botkin, Jeff Botkin, are you on the phone?

(No response.)

CHAIRPERSON HOWELL: No.

DR. LLOYD-PURYEAR: Ned Calonge.

(No response.)

Becky Buckley.

DR. BUCKLEY: I'm here.

DR. LLOYD-PURYEAR: Oh, good. We have a quorum.

Who just joined?

DR. BOTKIN: Jeff Botkin's here.

DR. LLOYD-PURYEAR: Oh, good.

Barbara Burton.

(No response.)

Freddy Chen.

(No response.)

William Hogge.

(No response.)

Sharon Terry.

(No response.)

Theresa Hart.

(No response.)

Tim Geleske.

(No response.)

Okay.

CHAIRPERSON HOWELL: Excellent. I think we'll start. As you remember, the Secretary, in responding to our letter on SCID, requested a report on the states' implementation of the recommendation to add SCID as a core condition, and also that that screening included key lymphocyte deficiencies to the list of secondary targets, including the surveillance activities conducted

through the Newborn Screening Translational Research Network.

Now, this report from the committee needs to go to the Secretary by May of 2011. We now are going to hear updates about the state implementation of SCID and various activities under way. I'm sure Jelili will bring this up, but certain activities were ongoing and active in the states at the time this recommendation was made and the NICHD issued a contract, a major contract, whose project officer is Tina Erd, and that contract went to New York State and there's been a lot of activities under that contract. We'll hear about I'm sure all of this as we go along today.

Mr. Jelili Ojodu is Director of the Newborn Screening Program at the Association of Public Health Laboratories here in Silver Spring, and Jelili is going to lead this session.

Michele has a comment, apparently, that's burning before that.

DR. LLOYD-PURYEAR: Sorry. Just a reminder for those who are going to join the committee for dinner, to make sure you please sign up after this session, before the subcommittee meetings. All the

committee and organizational representatives will find at their chair the report to the United Kingdom Health Technology Assessment on Screening for Critical Congenital Heart Disease. That report needs to be returned to me tomorrow. You also will find at your place a thumb drive containing the briefing book supplement.

CHAIRPERSON HOWELL: Let me add, the U.K. document you have that we've been fortunate enough -- Andy Ewer spoke at the conference we'll talk about a little bit later, but he was able to ask the U.K. to provide this draft document. It's not yet been published, so it's still a confidential document. That's the reason that the committee and liaison members have their name on the document, so that we'll retrieve all the documents, as we had promised to the group in the U.K.

I might point out, we would encourage you to join us tonight at dinner. The last time we had -- it's a very good restaurant. The last time we were there, Michele Obama was hosting a party at the same place, so we knew we had chosen a good restaurant.

Jelili.

NEWBORN SCIENCE FOR SEVERE COMBINED IMMMUNODEFICIENCY (SCID): STATE STATUS

MR. OJODU: Thank you, Dr. Howell. Good afternoon, everyone. Thank you to HRSA for allowing me to lead this session. It's actually an honor. I'm delighted to be here after the thunder-snow that we had over the past 12 hours.

Quickly, I have enlisted a number of folks to help me give you an update on what's going on as it relates to screening for severe combined immunodeficiency in states. So let's see here.

One of the four speakers that will be speaking this afternoon is Dr. Carla Cuthbert. Dr. Cuthbert will be giving a laboratory update, laboratory algorithms from the states that are currently doing newborn screening for SCID. Among other things, she would also be giving an update from the newborn screening quality assurance program as it relates to QC and PT materials.

She will also be giving an update on the total number of confirmed cases, at least up to date from those states.

Right after that -- I want to quickly check. Dr. Seroogy, are you on the phone?

DR. SEROOGY: Yes, I am.

MR. OJODU: Excellent. Dr. Christine Seroogy is an Associate Professor for Pediatric Allergy and Immunology at the University of Wisconsin. She will be giving an update from Wisconsin on follow-up activities and treatment protocols. Being that we have an hour for this session, it wouldn't make sense to do an update from all of the states, so we thought we should choose one of the states, and I chose Dr. Seroogy to give this presentation.

Right after Christine will be an update as relates to parent advocacy. There's no need to tell anyone here that the role of advocacy in adding new conditions to the panel, whether it's to state panels or to the recommended panel by the Secretary's Advisory Committee. It's very important. As such, we have invited Marcia Boyle, who's the President and founder of the Immune Deficiency Foundation, who will be talking about advocacy activities as well as educational materials that they have developed as it relates to SCID.

Marcia, are you on the line?

MS. MARCIA BOYLE: Yes, I am.

MR. OJODU: Excellent. Finally, someone who doesn't need any introduction to this committee, Dr. Mike Watson will be giving an update from the Newborn Screening Translational Research Network as it relates to the coordinated activities for what Dr. Howell mentioned earlier, which is the funding that came from NICHD to expand SCID testing in states.

So I think I'm going to quickly turn it over to Carla to get going here. We have an hour and I'm going to keep everyone to time.

(Pause.)

LABORATORY UPDATE

DR. CUTHBERT: I'm just waiting to get my slides set.

(Slide.)

CHAIRPERSON HOWELL: And they are up.

DR. CUTHBERT: And they are up.

Well, my name is Carla Cuthbert. Thank you, Jelili, for the opportunity to represent the states and what they have been doing.

As Jelili said, I was charged with giving -- with presenting an update on the experiences of the state laboratories. Just to remind you, to date all the

states that are doing screening have adopted the TREC assay, TREC being the marker that they are using for SCID. "TREC" again is short for "T-cell Receptor Excision Circles," and they are episomal DNA, DNA fragments that are not part of chromosomal DNA. So they don't replicate during mitosis. So with each cell division they are diluted within the daughter cells. So the peripheral blood level reflects the t-cell production in the thymus.

(Slide.)

Now, this particular assay was originally developed to assess thymic function in HIV-infected infants, but now it's been adapted to detect SCID and other t-cell lymphopenia in newborns. It uses real-time PCR-based approach and variations among the states in the assay can be based on their choice of primers and probes and their DNA extraction approaches.

There are currently four states that are performing this assay in house. The first state that actually got going was Wisconsin. Then there was Massachusetts, California, and New York. These are the states that I will be giving you very brief updates on.

Now, before I get onto this, what I'm actually

going to be presenting is, with each of the states, is just a very brief history and the current status, just a single slide, and then some of their data. If anyone's interested in their algorithms, I do have them. I just didn't want to go over that, given the time constraints.

(Slide.)

With respect to Wisconsin, their journey began in 2006, which was the end of that particular year. In November and December, the Jeffrey Modell Foundation and the Children's Hospital of Wisconsin provided $250,000 matching funds in support of the Wisconsin newborn screening SCID program. The Wisconsin State Laboratory of Wisconsin also provided an in-kind contribution.

In January of 2007, just a month later, they announced the Wisconsin newborn screening SCID program. Later that year, during that entire year, they began optimization of the TREC assay, and they started screening anonymized newborn screening cards.

In January of the year following, Wisconsin then launched routine newborn screening for SCID. So they are pretty much at three years of screening right now. From 2000 to now, they have demonstrated efficacy

of the TREC assay to detect SCID, and we'll see that in the next couple of slides.

Just to point out that in October of 2008 they received a three-year grant from CDC in support of their activities.

(Slide.)

Just to give the results of their testing. During the three-year period, the number screened that you will see representing the four states goes from their time of implementation of SCID testing to December 31st, 2010. That is a little bit of a typo. We're not anticipating how much they would screen until the end of this year, so that's 2010.

So the number screened in Wisconsin is just over 200,000. 18,000 of those infants are premature, so that's about 10 percent of the infants were premature.

In terms of abnormal results, they received about 160 using the algorithm that they used. 93 of those 160 were premature and 67 of them were full term. Inconclusive results were received on 288, and again of that the breakdown was that a significant number of those infants were premature. Again, they went through

their own series of algorithms and sent their samples out for follow-up, and their final results came back with five patients with severe lymphopenia.

These five cases break out as follows. They had one patient with idiopathic lymphopenia. Some regular IVIG and a bone marrow transplant is being planned. There's a patient with a Rac 2 mutation, with successful bone marrow transplantation. Idiopathic lymphopenia again, with bone marrow transplantation planned. There's a T-negative, B-negative, NK-positive SCID patient with a successful BMT, normal TRECs. Finally, there is an ADA SCID a possible gene therapy is being considered.

(Slide.)

In terms of evaluating the assay performance for these full-term babies, there is a sensitivity of 100 percent, meaning there's no known false negatives reported to date; positive predictive value of 40 percent, based on their Flow results; specificity of greater than 99 percent; and their detection rate for t-cell, severe t-cell lymphopenia, that would be the five cases in the 206,000 or so newborns, and that gives one

in 41,396.

(Slide.)

This just indicates the funding support that they currently receive. They are funded -- they have been funded by the Jeffrey Modell Foundation, Children's Hospital of Wisconsin, Wisconsin State Laboratory of Hygiene, and CDC.

(Slide.)

Let's turn to Massachusetts. Massachusetts again began their journey in March of 2007 with the formation of the SCID newborn screening working group. A little later that year, the development process for the multiplex TREC assay was begun, and from May 2008 onward they began work on IRB submissions and a statewide pilot update.

Again, Massachusetts was also the recipient of a CDC award, a three-year award that's going to be up this year. They received their award in October of 2008.

In February 2009 and onward, statewide newborn screening for SCID occurred, so that's their anniversary date. From September 2010 onward, they have been

engaging in screening in parallel, screening for SCID in parallel with Texas. Again, Texas is screening -- beginning to screen in this pilot, and they are just sending some samples to Massachusetts to correlate.

(Slide.)

So in terms of their results, they have had 143,000 or so initial specimens, and of these a little over 800 parents declined SCID newborn screening. There were over 800 again with no recorded consent for SCID and a little over 1700 had a program-wide unsatisfactory specimen submitted. So this resulted in 139,724 valid specimens that would be used for the SCID program.

You can see here, 120 were unsatisfactory for this assay. There were a little over 139 that were screened negative, 345 were screened positive, and of those, according to their algorithm, 29 were referred to Flow cytometry.

(Slide.)

So the next slide takes a look at that, those 29 cases. So these were abnormal SCID newborn screens and the infants were referred to Flow cytometry. Of those 29, 18 had an abnormal Flow result, 7 are pending

Flow. One had a Flow result within the normal limits. One case was closed and two were expired.

So of the 18 that had the abnormal Flow result, one was found to have SCID, four with DiGeorge syndrome, one with multiple congenital anomalies, and the rest were t-cell lymphopenias that are still undergoing testing. Three of those were not SCID -- well, three were not SCID and no further testing is needed.

SCID -- sorry. Six are not SCID and final diagnosis is pending in those six cases. Three, SCID is unlikely, and those cases are pending further workup.

The sensitivity is 100 percent. Again, no known cases have been missed.

Their funding support has been from the Centers for Disease Control.

(Slide.)

California. This began in July 2010, where NIH provided $480,000 for their SCID pilot program. All of the data from that program is going to be sent to NIH. The Jeffrey Modell Foundation also agreed to provide up to $800,000 matching funds in contribution to

the California newborn screening SCID pilot program.

(Slide.)

In August last year, the pilot program began, on the 16th of August. This is a very interesting model that was set up. It's called a lab within a laboratory. Perkin-Elmer staff is actually doing the testing of the specimens in a defined geographic location in the genetic disease laboratory facility.

In September 2010, again they are taking a look at their algorithm. It was initially very conservative at 60 and their cutoff level was dropped to 25. This month, again, they have been looking at one of their assays and have been doing some further refinement. They also decided to add nursery, a distinction between a regular nursery versus a NICU, to their flow charts.

In terms of their results, they have screened in the last few months that they have been operating -- and again, this is to December, the end of December 2010 -- 217,515 patients. There were 12 patients that were positive with this. Of those positive cases, four were SCID, one was DiGeorge, there was one with a non-SCID t-

cell lymphopenia, three with negative Flow, and three patients expired.

As far as the inconclusive results went, there were 229. Ten had a positive -- ten were positive, ten were inconclusive, and 127 negative, and this is with respect to Flow. 23 expired and 7 were lost to follow-up.

(Slide.)

We're going to take a look at the positive cases from the second heel stick. One wound up being DiGeorge, non-SCID t-cell lymphopenia; four were negative Flow cytometry; one expired; three pending.

Those that were inconclusive here, of them one was actually SCID. That was an interesting story. Two were negative Flow cytometry.

(Slide.)

So with a total of 217 initial specimens, 26 were referred to Flow cytometry, and here you see the breakout of the combined data. Again, Mike may probably like to discuss that a little bit more with you.

Their funding and support came from the Jeffrey Modell Foundation and from the National

Institute of Health.

(Slide.)

I'm going to get to this. This is just slightly out of order.

(Slide.)

So New York. They began in October 2009 to discuss the possibility of a pilot program with the North Shore Hospital. From the end of that year to April 2010, they visited with the Modells and had interaction with the Department of Health for in-kind funding.

From April to July last year, they optimized the TREC assay. During July of 2010 they got their laboratory configured and began preparation for the implementation of the SCID assay. In September they received finally their regulatory approval, emergency regulation and everything, and they began statewide screening in September.

(Slide.)

The number screened up until the end of last year was about 76,000, premature being a lot less, but fairly significant, about 10 percent, as with Wisconsin.

Abnormal results, they had full-term 223 abnormal results and 85 premature babies with abnormal results. For referral, that amounted to about 109. There were a number of samples that were unsuitable for testing.

(Slide.)

In terms of outcomes, one of the babies had leukemia and happened to be preparing for transplant. 18 of the babies were very ill and with diseases such as trisomy 21 CF cardiac anomalies, and Pena-Shakir syndrome, and meningitis. But of that particular group, one patient was found to have DiGeorge, one with Charge syndrome, three with idiopathic t-cell lymphopenias -- leukopenia, and one ADA deficiency. That just shows the breakout of the TREC levels.

Funding support was provided by NICHD, Department of Health, and the Jeffrey Modell Foundation.

(Slide.)

I'm just going to go back because my slides were out of order. With respect to the CDC, CDC continues to provide reference materials for these states and for all interested states or groups who would like to have materials for the TREC assay.

Dr. Vogt, who is in charge of this particular project, has materials for the screen-normal, screen-positive, indeterminate samples, and he has many dry blood spots ready for anyone who would like to use them. There are currently monthly send-outs to those states who are interested and groups who are interested. Five blinded reference dry blood spots are sent out. Currently there are about seven enrolled participants, which include of course the four states, Wisconsin, Massachusetts, California, and New York, Perkin-Elmer, and a laboratory in California.

(Slide.)

That's all I have to say. My last two slides are actually just an indication that there have been several publications, mostly from Wisconsin and Massachusetts, and I know that several are on the way.

(Slide.)

Thank you very much for your attention.

MR. OJODU: Chris, you're up. I'll move your slides for you. You just say "Next."

(Slide.)

FOLLOW-UP AND TREATMENT UPDATE

DR. SEROOGY: Thank you.

I'd like to thank Jelili for inviting me to present our experience at the University of Wisconsin in the newborn screening for SCID. I'm going to present cases that we've managed at our hospital over the last seven months. I think they exemplify the success of the program, the challenges, and also the spectrum of SCID disease.

Next.

(Slide.)

The first SCID infant that I will discuss was born at term via uncomplicated delivery, to parents that were unrelated. The infant had his newborn screen drawn on day of life number one and left the hospital on day of life number two.

I was contacted when the infant was eight days old by the Wisconsin State Lab of Hygiene because of an abnormal result for the SCID screen. The TREC value on that initial sample was zero, and because of that undetectable value we arranged for Flow cytometry that day.

Next. (Slide.)

The Flow cytometry on this infant demonstrated profound lymphopenia, with very low t-cell numbers, a value of 111, with the lower limit of normal for this age being 2500; also, very low B cell numbers, with an absolute value of 28, again extremely depressed, with the lower limit of normal being 430.

This infant did have normal NK cell numbers. When we looked at naive T-cells that are a correlate of thymic function, we found that of the circulating T-cells very few of them were of the naive phenotype. Additionally, the filter card was repeated on this Flow sample, and again the TREC value was zero.

So our conclusion based on this finding was that this was consistent or highly suggestive of the T-minus, B-minus, NK-positive form of SCID.

Next.

(Slide.)

This child, for further evaluation and because of the abnormal Flow cytometry, was brought into the American Family Children's Hospital and put into protective isolation. We initiated anti-microbial

prophylaxis, intravenous gamma globulin. We suspended breastfeeding because we did not know the CMV status of the mother, and diagnostic testing ensued.

Next.

(Slide.)

This is a slide overviewing all of the diagnostic tests that were done, including genetic sequencing by commercial laboratories as well as research laboratories through Dr. Jennifer Puck and her SCID chip. We also were concerned about a radiosensitive form of SCID based on the phenotyping and obtained skin cells early on to perform radiosensitivity testing, which I'll get to in a subsequent slide.

We looked at T-cell function and any evidence of maternal engraftment that would impact treatment decisions. We also, despite thinking it would be unlikely, did biochemical testing for adenosine deaminase form of SCID and that was sent to Duke, Dr. Michael Hirschfield's lab, and that was normal.

Next.

(Slide.)

Gene sequencing was done as rapidly as could

be done through the efforts of many people. Here's the list of the genes that were sequenced and did not reveal any deleterious mutation. We did get this data back over a four to five weeks time and did not find any genetic mutation for a lot of the commonly described genes associated with SCID and the type that we would be concerned about with this phenotype.

Next.

(Slide.)

Once our skin fibroblast cell line was established, it was sent to two labs, the laboratory of Dr. Richard Gatti as well as Doctors Moore and Cowen, at UCSF and Berkeley research laboratories. These data I want to point out were not available until ten weeks of age for this infant, given the rigors of this type of assay.

But what's shown here -- and I'll direct you to the right side of your screen -- is that our patient does have a component of radiosensitivity. This is a functional assay to look at the ability of fibroblasts to survive when they're subjected to radiation.

I'll also point out that our patient, if you

compare him to known radiosensitive forms of SCID, does not appear to be, at least from the UCSF data, as severely affected as an Artemis form of SCID or a DNA ligase 4 form of SCID.

Next.

(Slide.)

While we were waiting for the diagnostic testing to become available, we wanted to ascertain that this was indeed a stable phenotype of T-minus, B-minus, NK-plus skid. The way we approached that was by doing serial Flow cytometry, and that data is shown here. What you will see as far out as 45 days of life, our patient had persistently, profoundly diminished T and B-cell numbers, with maintenance of normal NK cell numbers.

So we were confident that this was a classical presentation of SCID of the T-minus, B-minus, NK phenotype.

Next.

(Slide.)

We then were faced with the decisionmaking process for a curative approach. There are multiple

considerations that go into this decision. One of course is the timing of transplant. Data, particularly from Dr. Buckley's group, have shown that timing is very important, that early leads to better outcomes, specifically under three months of age. That's probably for multiple reasons, including the age of the patient promoting better engraftment, as well as if you do it early you less likely have preexisting conditions, such as infections, which can impact the outcome in engraftment.

The donor source is also important. The best donor for hematopoietic stem cells would be a matched sibling, which was not an option in this case. Then you're faced with other sources, such as a parent's donation, a match-unrelated donor, or umbilical cord blood. The literature is less clear on the best approach for SCID.

Then the other important consideration is approach to transplantation, and that is the need for conditioning to prepare the patient for the transplant. Again, that is dependent on the form of SCID as well as the donor source.

Next.

(Slide.)

We, given our scenario, searched donor marrow registries and were fortunate enough to find a very good cord blood match for our patient. Given that we were using cord blood and the type of SCID that we were dealing with, the decision was made to use a reduced intensity conditioning regimen, as is shown here. This was undertaken when the patient was eight weeks of age.

Because we were using an unrelated donor source, the patient also received graft-versus-host disease prophylaxis as is noted.

Next.

(Slide.)

So in order to monitor for engraftment, we did engraftment studies at the molecular level, which demonstrated engraftment over time. We also monitored Flow cytometry to look at immune cell number normalization. That's what's shown on this slide. Serial Flow cytometry, the latest data I have presented here is 92 days after transplant, do show improvement in T-cell and B-cell numbers as well as NK-cell numbers.

I'll also tell you that the patient is now 180 days out from transplant and his last Flow cytometry demonstrated normal immune cell numbers, including normal naive T-cell numbers, which suggests thymic function.

Additionally, we've done the dried blood spot TREC analysis on the most recent Flow cytometry and it demonstrated normalization of his TREC values.

The summary of the first SCID patient managed at our facility is he was translated on day of life 77, tolerated the procedure well. He was sent home in stable condition on day of life 107 and now, over 6 months out from transplant, continues to be clinically stable, with normalization of his immune cell numbers.

His molecular diagnosis still is unknown, but there is a very active ongoing investigation. This case may represent a novel mutation of perhaps a previously unknown presentation of a SCID-associated gene.

Lastly and I think importantly, this case does provide evidence that implementation of TREC analysis on newborn screening could identify a SCID patient early to allow for successful transplantation, while minimizing morbidity and mortality.

Next.

(Slide.)

The second patient at our facility was known to me to have a family history of severe combined immunodeficiency, but was blinded to our patient lab. Because of this, cord blood was drawn in the delivery room, and that data is shown here. A filter card was obtained shortly after the newborn period and sent to the state lab.

His initial blood count showed profound lymphopenia with almost completely absent T, B, and NK cell numbers. The dry blood spot TREC value was zero on this patient. We were concerned, based on the family history, that this was an ADA form of SCID. From the cord blood, biochemical testing was sent to Dr. Michael Hirschfield and we had confirmation of this within 48 hours, that this was indeed an ADA form of SCID.

This patient was sent home in protected isolation, was started on enzyme replacement, which is available for this form of SCID. He received PEG-ADA. He also received antimicrobial prophylaxis and intravenous gamma globulin. We were able to continue

breastfeeding in this case because we were able to test mom for CMD while she was pregnant.

Next.

(Slide.)

When we were monitoring for the therapeutic benefits of the enzyme replacement therapy, we were able to follow toxic metabolites via Dr. Hirschfield's lab at Duke. These are data serially looking at that, showing that the enzyme was working and that it was decreasing the toxic metabolites that caused the profound lymphopenia in this case.

Next.

(Slide.)

We also did serial Flow cytometry and showed that, while enzyme replacement in this infant did have improvement in his lymphocyte numbers -- if you look at day 60, his T-cell number has now increased to 451 -- I'll also state that he is still profoundly immune-compromised.

Next.

(Slide.)

In summary, the second SCID patient identified

managed through our hospital continues to grow and thrive. He remains infection free. The plan in this case is for him to proceed to gene therapy at the NIH. That will occur once he reaches ten kilograms, which is the entry point for their protocol. We're hopeful that that will occur over the next two to three months.

Next.

(Slide.)

I think, comparing and contrasting these two cases, they do span the spectrum in that SCID patient number one has a molecular, undefinable at this point in time, form of SCID. It's a rare form of SCID that's seen in this country and represents approximately 5 percent of SCID cases, and that is T-minus, B-minus, NK-plus. This patient initially was evaluated and worked up in the hospital.

In contrast, SCID case number two, there is a rapid metabolic test to screen for the genetic defect and that's for ADA deficiency, which allowed rapid identification. He was sent home in isolation, was given enzyme replacement, which decreased the toxic metabolites and also improved immune function.

Hematopoietic stem cell transplantation in ADA SCID is quite -- has very good outcomes when there's a matched sibling, but when there is not a matched sibling the data is less clear. For this form of SCID, there are open protocols in this country as well as abroad for gene therapy, which this patient will undergo in the near future.

In summary, I think these cases exemplify the success of the screening program and they also highlight some of the present challenges. One is the duration to follow a genetically undefinable form of SCID to ensure the phenotype and move to curative approaches, which is important to do as quickly as possible. In our experience, the TREC value of zero seems to be a very robust indicator that this is indeed classical form of SCID.

The other challenge is to develop a rapid radiosensitivity test, because that does impact the approach to cure.

Then lastly, the challenges on the decisionmaking regarding donor selection for a curative approach and the approach to that cure, which is an

still ongoing investigation.

Thank you for your attention.

MR. OJODU: Thank you, Chris.

Can you please load Marcia's slides. Thank you.

Ms. Boyle, you're up.

(Slide.)

PARENT ADVOCACY/EDUCATIONAL MATERIAL DEVELOPMENT

MS. MARCIA BOYLE: Well, thank you very much. Jelili, thank you very much for asking me to participate, and I particularly want to thank the Advisory Committee for last year making the recommendation to add SCID and key lymphocyte deficiencies to the panel for newborn screening. Obviously, we're delighted with the Secretary's agreement with your wise decision.

We have been -- well, let's go to the next slide. Sorry.

(Slide.)

I do apologize for not being there in person and I would like to have been.

The mission statement. As you know, we are

the national patient organization for the primary immune deficiency diseases.

Next slide.

(Slide.)

Just a little bit. We are small, but we certainly are a very busy organization, as you can see. Newborn screening for SCID is one of our very important initiatives and something that we're in for the long haul here. So it's exciting to just be able to give you a little update on what we're doing for advocacy and the partnership that we feel we have with the whole community on making this take place.

The next slide.

(Slide.)

I was very pleased to be able to present two years ago from a survey that we had conducted among our SCID families. Just as an update to you -- and I think you have, the members of the committee have, a handout -- the results from this were published in an article in Clinical Immunology. I think you have a copy of that. Some of the major findings from the survey are outlined on the slide, but the bottom line is we're certainly

using some of the findings from this survey of our families in our advocacy, and it's been extremely helpful to us to have this data.

The next slide.

(Slide.)

Obviously, once the Secretary agreed to include SCID in newborn screening panels we really launched our campaign. It's been taking up a great deal of our efforts. Current status of implementation; you have been updated on this, obviously. The second bullet, the states where the newborn screening advisory committee voted in various states to recommend the addition of SCID, but screening has not yet begun. Obviously, Colorado, Minnesota, Delaware, North Carolina, Iowa, Michigan, and Rhode Island. We're very excited about the progress we've been making in some of these states.

As far as our activities, last summer, frankly, we brought in an intern that helped us call and survey all of the state health departments regarding the process for adding the condition to their screening panel. So with that information, we would have a better

idea of how to approach a state. We've had conversations with a number of state health departments, provided resources, cost analysis figures. We've given recommendations in some states for expert immunologists that they needed in order to move ahead, and we've been pleased to do that.

Where we can, we form alliances in states to help along the newborn screening. Very importantly, we've worked very closely with our volunteers. Many of them are SCID families, but others are just volunteers with a primary immune deficiency who feel very strongly about this issue.

Next slide.

(Slide.)

We've been active in about 30 states. As we mentioned, about five advisory committees have voted to recommend SCID based on our volunteers. We're currently involved in the following states. I'd like to underscore the state of Florida, where tomorrow the advisory committee is meeting. Actually we're bringing -- we have a very active volunteer there -- bringing busloads of people, have an immunologist who's

testifying, and they've actually had to change their venue with the number of people coming. So we have great hopes for Florida being added to the list of states, of advisory committees that are recommending SCID. So stay tuned for that.

As far as our educational activities, you can see from the next slide our idea, "SCID: Take Action." We actually developed our own logo for this. If you have not seen our SCID newborn screening campaign web page that's listed at the bottom of the slide, I urge you to do so. We have developed a toolkit for educating policymakers that I believe the committee members have a copy of. I hope you do. I know we sent it in. This has been important for our volunteers, background information, how to go about the advocacy.

Our newborn screening blog, again take a look at it. It's a very active blog that we keep up to date from our office, for all the activities that are going on around the country, where our volunteers are testifying and making a difference.

We created and distributed a brochure on live rotovirus vaccine to warn providers about the dangers of

administering the vaccine to infants with SCID. That really came about because of our testimony in Florida and the concern they had, and that has been distributed to all pediatricians in Florida and is posted in some other states, and we are in the process of getting this brochure out to others, all 50 states.

We were very honored to present at the CDC meeting in Atlanta to all 50 state lab programs last October and have had many good conversations, follow-up conversations, since. We produced two videos of SCID parents, because we can't always bring the parents and the stories to every meeting, just emphasizing from the human perspective the importance of early detection, and again it was shared by Heather Smith, who developed it, at the CDC meeting.

Next slide.

(Slide.)

It just shows copies of our newborn screening toolkit, the rotovirus brochure that I think you all have a copy of as well, and a snapshot from our newborn screening blog.

Again, the next slide.

(Slide.)

The videos are on YouTube, on Facebook, they're on our site, and we're using them extensively. If you haven't seen them, I think you would be very interested to see these stories. I think you have met Barb Ballard before. She has testified and Heather I think has testified by phone, and very compelling stories.

Next slide.

(Slide.)

The challenges to implementation. Obviously, funding is the major barrier. The cost estimates that you see, $500,000 to a million to the state. Those are statistics from Wisconsin and Massachusetts. In some cases, we've been told that you've got to wait your turn, there's a prior commitment to other disease groups. Obviously, the need to set up a protocol for follow-up within the state for a positive screen. In some cases, we've heard the current lack of an FDA-approved assay for the screening may be a challenge.

Some of our recommendations -- next slide --

(Slide.)

-- is states must develop networks of specialists, obviously, in primary immune deficiency for diagnosis and treatment. The states must develop strategies to ensure patients access to specialists, including sending patients out of state to medical centers with expertise in bone marrow transplantation for SCID, when such resources are not available in the state. We have heard some instances of state Medicaid programs reluctant to approve a state going out of state, so that is a concern that we have and that has to be dealt with.

Next slide.

(Slide.)

As far as educational needs in a state, states need to develop systems to educate and communicate the next steps to physicians and families. We understand pieces are being developed for pediatricians following identification of a positive test result. It's extremely important to have the communication. Educational piece for parents who receive a positive screen; what does it mean, what to do next on receiving a diagnosis. That's something we are working on

developing ourselves, and we'd love to partner on, obviously, with others, as well as an educational piece for parents who do receive a definitive diagnosis, so kind of two different educational initiatives.

The next slide --

(Slide.)

-- does show we already have a great deal of information from our patient and family handbook that's on our web site and also available to anyone who asks on SCID and the treatment of SCID. This is something that we are in the process of updating our online version to include more information on other severe T-lymphocyte disorders. This also has information on DiGeorge syndrome.

So again, developing educational -- next slide --

(Slide.)

-- educational materials for families who receive a positive screening result. As I indicated, we are working with a specialist to develop kind of a brochure that we hope the states can either use or adapt to educate parents who have received a positive screen

and that will explain what SCID and other T-lymphocyte deficiencies are and appropriate treatment, relieve concerns by explaining what to do next, and give links to resources, additional resources on SCID and other T-lymphocyte deficiencies.

I want to thank you very much for having this opportunity to update you on some of the initiatives that we have undertaken in the last year, and we look forward to doing everything we can. Thank you very much.

MR. OJODU: Thank you, Ms. Boyle.

Mike.

NBSTRN UPDATE

DR. WATSON: Hi, Gerry.

DR. VOCKLEY: Hi.

DR. WATSON: Poor Gerry, drove all night to get here from Pittsburgh.

DR. VOCKLEY: I didn't drive, unfortunately. I sat all night to get here.

(Slide.)

DR. WATSON: The NBSTRN update is really as much to update you on what the NBSTRN is doing both in

SCID and a number of other conditions. The fundamental goal, obviously, of the NIH is research investigation and sort of the science side of screening and the conditions that we screen for.

I think I want to acknowledge one person, Amy Brower, who's in the audience. Amy has really been the one who has led this particular workgroup doing all the SCID work for the NBSTRN and has put in a tremendous amount of effort and time. So I want to thank her for all the work she's done. It's difficult pulling a large number of states and different research groups together in studies like this, and she's done a very nice job.

One of the fundamental interests in the NBSTRN has been initially to build an infrastructure that supports highly collaborative research. We want it to be highly protocol-driven because that's the only way we can actually get multiple investigator groups and states to bring compatible data to the table so that we can begin to learn more about these very rare conditions.

So the first years of the NBSTRN have been focused on building that infrastructure and the resources to support the ability of investigators to do

this kind of work.

(Slide.)

The NICHD had issued a subcontract to New York State back in early summer, so we're actually not very far into our studies, and much of the data has already been shown to you by Carla Cuthbert from California, which has -- obviously, a state that size generates a serious amount of data in a fairly short time. They began their screening really in about August or September and are 200,000 babies in now. 19 have been sent to Flow. Four babies died before they got subsequent testing done. Given the timing of all these, we have very little data available now about these patients, but we'll be bringing that into our database and we can present that to you at a later time.

The four laboratories that are funded by this New York State subcontract are: obviously, New York itself, which will do about 80,000 babies under the contract; California that's doing a little less than half a year's worth of screening in 200,000 babies. Louisiana will be doing screening through the Wisconsin laboratory that had already established expertise in

screening for SCID. And Puerto Rico will be doing their screening through the Massachusetts laboratory, which similarly had been funded and had developed the expertise in screening. You can see the numbers of babies roughly that they expect to be screening.

(Slide.)

The NBSTRN coordinating center itself, which we operate, supports a number of activities related to the New York subcontract. The New York subcontract largely funds the per-baby screening, and that's something we really wanted to maximize, and we did that by supplementing their funding with the NBSTRN's core funding that allowed them to bring the experts together for meetings. We supported a number of resource development projects, which I'll show you. Some of them are existing projects you've heard about previously, that we've adapted to some of the needs of working in a pilot environment as opposed to sort of a retrospective look at performance of newborn screening laboratories as a means of improving them, and are adapting our tools to really be used prospectively in pilot studies that allow many states to bring their data together, learn from

each other, generate much larger data sets, much more rapidly, and hopefully identify the difficulties and the laboratory complexities much more rapidly by having collaborated and pooled their data together.

(Slide.)

The main activities that we've been involved in is, first, that infrastructure to support this collaborative approach to pilot studies; the resources and the infrastructure that we're developing around clinical data sets that describe the protocols by which diagnosis is established, by which treatment is done, and by which monitoring of those patients over the long term is done, and that really allows us to get a longitudinal health record look at a patient, not just at a point of time of screening, but longitudinally through the course of their treatment and management.

There is currently an RFP out, or actually it's at the very end stage of finding who's going to get the grants. But the NICHD has an interest in developing the clinical histories of these conditions. SCID screening is a lot like hearing screening in that there are a whole bunch of potential conditions that can be

diagnosed and they're exceedingly rare. Unless we pool our resources and data together, hopefully in an organized, protocol-driven way that allows for some compatibility of that data, we'll have a much better sense of really what all these rare causes of both no-SCID -- I'm sorry -- no-TRECs and no-TRECs types of findings are all about.

We're in the stage now of putting the final disease-specific parts of the protocols together for SCID. Because we're building an infrastructure and resources, we focus a lot on taking those diagnosis, follow-up treatment languages and bringing them into the national electronic health system language standardization process, which then drives all manufacturers of EMRs and other things to accept those as the language standards, and they become integrated into the electronic health system of the United States, which then gives them a secondary set of legs of really having compatible data that we can draw from many places over time.

(Slide.)

The IT and the informatics have been very

important in the NBSTRN's development in order to support the point of care data collection. It's clear to us that providers don't want to do things more than once. If they have to capture the information about their visit with the patient, they'd like to capture it at the point of care. They'd like to be able to share it with their electronic medical record in their institution if they have one or whatever medical record system is available. They would like to be able to share it with registries that might be part of a phase 4 surveillance process if there's an FDA-approved drug in place for a very rare disease.

So there's a number of directions that these kind of data go that are tools are going to be able to push to the registries, push to the institutional databases, in the hopes that it keeps the impact on the physician at the point of care at the minimum.

We're in the process of developing ACT sheets that guide the primary care providers. In many states, as screening evolves they'll be the first ones that may find out about a screen positive baby and they'll have to move them into a system in which the experts in T-

cell lymphopenia, these types of disorders, are able to see them and move them through diagnosis and treatment.

We also want to be able to develop broad directories of the clinical specialists in these conditions, partially because there's a number of states, obviously, already screening. There's a larger number of states that are about to begin screening. Just in our calls alone, there have been an additional four states who have begun to participate because they're in fairly far-along planning to get into SCID. That's Nebraska, Delaware, Colorado, and Minnesota, and their data will be able to come into these databases as well.

(Slide.)

The SCID expert group is developed on the model that we expect to be that for all the kinds of studies that are involved in the NBSTRN. We are the coordinating center and we support the investigators, who have expertise in these disorders. So Michele Caggana, who is now the chair of this group -- it actually started as a subcontract in which Ken Pass was the PI. Ken retired in late September and we went

through a period of transferring the responsibility for the subcontract to Michele Caggana.

The members, you can see, of that expert group are listed there. People from immunology, pediatrics, biochemical genetics, immunology, newborn screening are all involved in this expert group. It's the one developing sort of the measures by which we'll collect the newborn screening data itself, as well as the diagnosis, treatment, and follow-up data sets that are going to be part of the long-term studies.

(Slide.)

One of the first tools we adapted was the R4S database that Dr. Piero Rinaldo has presented to you previously. Something like almost all states and another 40 countries are bringing their newborn screening data into this particular database. It has been of tremendous value to a large number of states as a quality improvement tool, and it seemed apparent that we could readily adapt that tool to prospective use in pilots. It's basically the same kind of data. It's just at the earliest stages of the development of the screening as opposed to after it's well established.

Those databases are being curated by Doctors Fred Lorey and Roshini Abraham, both of whom have, one in newborn screening and one in immunology, expertise in the T-cell lymphopenias, with Dr. Rinaldo's group taking an administrative role and guidance from these experts involved in this particular project as to the data sets that are going to be appropriate to develop for that particular tool.

The first data is just coming in, actually. I took this picture prior to the data coming in. California, as you heard, is well along and their data is coming in now. But you've basically seen this framework before. It shows you some of the analytical parameters, some of the display tools that are going to be available for those participating in SCID screening.

(Slide.)

On the diagnosis and follow-up data set side, we're still in the development stage. We're building off a much larger project that involves all conditions in newborn screening that Dr. Sue Berry has led, along with others from the NBSTRN coordinating center. They've gone through a long iterative process of

reaching consensus on some of the core aspects of data collected at the point of care. These are the data points that are all shared across all conditions in which we have an interest in developing protocols.

So there are a large number of data points within each of these general categories, from demographics, socioeconomic status, family history, prenatal history, neonatal history, birth measurements, the newborn screening data itself, the dianostic testing data, past health history, emergency management of patients, developmental screening, and imaging studies. That's about 80 percent or so of the data points acquired at the point of care.

To that, we then supplement the data, the disease-specific data points, in a highly protocol-driven way in the hope that the data is much more compatible, because that's really one of the things that underpins the success of the national cancer cooperative study groups, was expert-developed, protocol-driven kinds of activities on the clinical side that allowed for data to be pooled and actually have both longevity and the ability to have larger data sets, critically

important in these very rare conditions.

To develop the disease-specific data sets, we're largely working with the primary immune deficiency treatment consortium. It's a group that's been funded under the Office of Rare Diseases, Rare Disease Clinical Consortia. It's a model we're also using for the lysosomal storage diseases, which allows us to identify people who are already funded to work in these areas and allow them to work within the tools we're developing to get both the expertise and the sharing of the tools that allow for them to collaborate together, and at this point not necessarily have to use their own grant money, but generate the data that will allow them to be competitive, to bring these kinds of studies in under their consortia over time.

(Slide.)

On that, I'll say thank you. We're still in that -- we're only four or five months in, so I can't give you patient-specific data, but we can do that at a later meeting if you so desire.

MR. OJODU: All right. Thank you to all of the speakers. Actually many thanks to all of the

speakers for taking their time to present here. I'd like to thank also IDF. We actually invited the Jeffrey Modell Foundation to be part of this panel and, due to unavoidable circumstances, they were not able to attend, but they did provide quite a few information that I will be talking about later on. As you know, they have been actively engaged on many levels, whether it's federal, state, or local levels, in moving newborn screening forward in states.

I'd also like to thank Lisa Vasquez from HRSA for all her help.

Just a quick update in reference to meetings. I think it was October -- this was referenced a little while ago, but we, APHL, CDC, HRSA, and the National Newborn Screening and Genetics Resource Center hosted a meeting, a national meeting on newborn screening for SCID, implementation, challenges, and updates.

For the committee members around the table, you should have a link in, I don't know if it's a binder or if it's on your thumb drive, that will take you directly to the web site. This was well attended, well received, and it was actually an excellent meeting.

Close to 200 participants from around the country and from three -- I mean, from around the United States and three countries, laboratorians, follow-up coordinators, and immunologists.

You will be able to find the archive videos that will play simultaneously with the slides that were presented for all of these presentations on our web site. So I would encourage anyone who wasn't in attendance at that meeting to please see these presentations.

Another quick update here is, I think we have an onus to actually increase the work force as it relates to newborn screening and in particular SCID, in memory of a pioneer, Dr. Ron Laessig. The Jeffrey Modell Foundation, the Centers for Disease Control and Prevention, and APHL currently support a fellowship in Ron's memory. Dr. Held actually just started at the University of Wisconsin -- I mean, the Wisconsin State Public Health Lab -- on January 3rd. I think this is excellent. This was at the suggestion of Dr. Hannon and Dr. Vogt from the CDC. This is a two-year postdoc fellowship and we hope to be able to continue these

kinds of fellowships that will be moved around, available from state to state, in the near future with the funds available.

I think, in summary here, you've heard that four states do screen for those -- I mean, six states do screening for SCID right now: New York, Wisconsin, Massachusetts, California, Louisiana via Wisconsin, and Puerto Rico via Massachusetts.

(Slide.)

This is just a map representation of those states. Right now you also heard from several of the presentations on activities, whether it's state public health labs or public health departments that -- states where the advisory committees are actively engaged in adding and recommending SCID to their newborn screening panels. I've added those states to the list here. It depends on how you count them or how you read what's going on, but they can add up to between 9 and 12 right now. SCID is pending in these states.

Then I think a lot of people are still considering to add SCID to their panels. I think they're thinking about the economic climate, among other

things, and the current state of things. I was telling Michele this the other day, that we have 24 new governors, and those 24 new governors will mean that we'll have 24 new health officials, and there will be a repercussion that will drop down to state public health labs and newborn screening programs across the country.

How this will affect implementation of SCID is yet to be seen. But this is not only for SCID. It's for all these conditions that the advisory panel -- that the Secretary's Advisory Committee adds to the core panel of conditions. So as you add those panels, please consider the financial implications on the states that are going to be doing this.

That's it for me. Thank you.

CHAIRPERSON HOWELL: Thank you very much, Jelili.

Unfortunately, we are running a little over time. But one thing I would like to do. The very large amount of money that's been put into the pilot studies from the NIH has been to a subcontract to Michele Caggana, and I wonder, Michele, do you have anything to add? Your work has been presented repeatedly. Do you

have anything to say about your work? Were you properly represented?

Come to the microphone.

DR. CAGGANA: Just that it's been a quick learning curve and that it's been really great working with the states, with Fred, Ann, and May, and then, as Mike mentioned, getting together with some of the other states that are in different stages of considering or having approval to add SCIDs.

From a laboratory point of view, it's been really helpful. I've learned a lot from Ann and May. Fred and I kind of came in as the newbies and so it was really a good experience for us. The ability for the funded states to be able to put data into the database for the specimens that they are testing as part of this I think will help us understand SCID and the different types of conditions.

You heard that there are a couple of different new SCIDs that are being picked up just by screening, so we're learning a lot as we go.

Lastly, it's been wonderful also to have help from the NBSTRN, from Amy, who I email pretty much every

other day or so, and Arena, and also Dr. Buckley, Dr. Puck, and Dr. Abraham from the Mayo Clinic. So the clinical input has been great and the collaboration between the states has been great, too.

So thank you.

CHAIRPERSON HOWELL: Well, I know your project officer at NIH, who's Dr. Erd, has found it a pleasure to work with you. It's been exciting to see how rapidly your group has been able to bring hundreds of thousands of newly screened babies to the table.

Finally, the other person whose work we've heard a great deal about, but nothing from her, is Amy Brower. Amy, do you have anything to say?

DR. BROWER: Oh, it was represented better than I could have done it myself. Thank you, Mike.

It's been a great experience, I think, for really trying to learn from the SCID recommendation and the implementation how we can get ready for the LSDs and for the other conditions that are currently being nominated. So we're sort of using it as a platform to showcase the NICHD-supported NBSTRN, as well as continue our work on the long-term follow-up data set, which is a

great joint effort between HRSA and NICHD. So we're learning a lot, as Michele said. She doesn't mind when I email her every day. She just answers me every other.

CHAIRPERSON HOWELL: Finally, I wonder if Tina Erd has anything to say. She's the person at the NIH that works on getting the money to flow and trying to keep it all legal.

DR. ERD: We're not a shy bunch. We're not afraid to say things. I guess the one thing I'd like to add is that the way we've set up the contract is, even though the money for the blood spots will be -- there will be an end to that amount of money, we're setting up a system that the new states that are being added can continue to learn from the states that had experience. It's kind of like a support group. They're listening in while the other groups are setting up.

There's a place to put in the data. I think they haven't talked about the system nearly enough. It would have been nice to hear a little bit more about that, because that's very exciting, how they're coming to consensus on decisions, so as the new states come in there's consensus information; it will go

much more smoothly and more easily as people come on board.

But I think everyone's done a very nice job working collaboratively. It's been a good experience.

CHAIRPERSON HOWELL: Let me make one comment. That is that this Advisory Committee, as you know, looked at all the evidence and made a formal recommendation that this condition should be added to the core panel, and at the same time we felt that before everybody in the United States started it would be important to look at a lot of babies. Fortunately, the NIH came to the table with a big chunk of money to help do that, and everybody in the room has worked on that. I think that now once these pilot data are available and we have hundreds of thousands of babies who've been screened in state labs, the information will really be available now that would enable states to adopt this recommendation.

I think this is the way the adoption should go. In other words, the adoption should go once it's truly ready to go prime time and once everything is ready to go. I'm excited about that.

Michele has a parting word, but we do need -- or maybe Jelili has a parting word. But we need to quickly part for our next thing.

DR. LLOYD-PURYEAR: One important part of the Secretary's acceptance of this recommendation was a report that's required from the committee in May of this year on the current state of the states of implementation. So I would like to know what entity, either CDC or NIH or a collaborative effort, is going to take responsibility for writing that report.

CHAIRPERSON HOWELL: I'm sure there will be many volunteers. We don't need to decide that right now, do we?

DR. LLOYD-PURYEAR: We do need to decide that now. I need to decide that now, I do. Tina, can you lead that effort?

DR. ERD: I would like to just make it a collaborative effort between CDC and NIH. I'm sure, if Carla is agreeable, we can all work together on this.

CHAIRPERSON HOWELL: I think a great team would be Carla and Tina.

DR. CUTHBERT: Yes, we'll join in.

DR. LLOYD-PURYEAR: So we would have a first draft of that by April 2011, April 1st?

CHAIRPERSON HOWELL: Those two worker bees will have no problem doing that.

Jelili, one quick comment.

MR. OJODU: It's just another thank-you. Thank you to the pioneers from the states, even though they weren't here to give the presentation. You know them. You hear their names all the time: Ann Comeau, May Baker, Fred Lowery, and the rest of the folks that have been doing a great job of making sure that we educate others on SCID testing. And the funding agencies, of course: CDC, NIH, and HRSA.

Thank you.

CHAIRPERSON HOWELL: As we depart, the Follow-Up and Treatment group will be meeting here in this room. So the folks who are not a member of that group should get out of here quickly.

The Laboratory Standards and Procedures group will be meeting in City Center 1, which is off to the left; and the Education and Training will be in City Center 2, which is right next door to the left. The

Health Information Technology Workgroup will meet between 5:15 and 5:45 in City Center 2.

Otherwise, we'll see you cats in the morning.

(Whereupon, at 2:29 p.m., the meeting was adjourned.)