Severe Combined Immunodeficiency (SCID) Webinar

January 2017

Please direct all comments/ questions pertaining to this webinar to Ruthanne Sheller at Rutahnne.Sheller@aphl.org or 240-485-2767

Marci Sontag: Good afternoon everyone and welcome to the January 2017 SCID National Quarterly Webinar. On behalf of NewSTEPs and Newborn Screening Translational Research Network I'm excited to welcome you to this webinar. We have a great agenda set forth. This is Marci Sontag and we are very happy to have you all here today.

I am going to very quickly go to our agenda. We're going to begin by reviewing the SCID Newborn Screening Status Map and then we will have a clinical vignette on Newborn Screening for SCID presented by the Dr. Kate Sullivan who I will introduce momentarily. Then, we will have Sondi Aponte present the current progress that they are making in the State of Arizona for SCID implementation. Then, at the end we will have time for questions and discussion.

The conference is not muted for all participants so as we move forward if you would like to ask a question and for the presenters if you can press *7 to unmute yourself. As I said, we will begin with the SCID Newborn Screening Status Map in the United States, DC and Puerto Rico. We're very excited to announce that Missouri is now screening all newborns for SCID. We're getting closer and closer to having a fully purple map. It's very exciting to see the progress that is being made in the United States for SCID newborn screening.

With that I'm going to very quickly turn it over to our first presenter. Dr. Kate Sullivan is a professor of pediatrics at the Children's Hospital of Philadelphia. She has worked on SCID advocacy and has worked very closely with the Pennsylvania Newborn Screening Program to implement SCID and to follow children who are diagnosed with SCID or with an abnormal newborn screening. Dr. Sullivan I will turn it over to you. You can press *7 to unmute.

Dr. Sullivan: I think I have unmuted, can you hear me?

Marci Sontag: I sure can.

Dr. Sullivan: Excellent. We'll go ahead and get started. Thank you so much for having me. This is really exciting. I will say before I start that I'm going to give you a little background on newborn screening for SCID, which may be familiar to some of you already and then end with a few vignettes that are near and dear to my heart. Before I get started the other thing I would like to say is that newborn screening for SCID has been the single most transformative thing to happen in

my career. I've been an immunologist for over 20 years and I can't think of another thing that has changed my practice more than this has. I'm an unabashed fan of this and I think it will come through in my presentation.

As I said, I'm just going to start with a little bit of a background about SCID. It is an inherited immune deficiency and it uniformly presents in infants. There are variations on the SCID scene that can present later in life but truly to have severe combined immune deficiency or SCID is a disorder in infants. It is fatal if untreated. Newborn screening is designed to move up treatment and I'll show you some data that compares the pre-newborn screen era with the current era. Transplantation is the gold standard for treatment although I'll say just one word about gene therapy towards the end.

Among all immune deficiencies about 15% correspond to T-cell immune deficiencies in the US, in Europe it's slightly lower. This is registry based data and severe combined immune deficiency is the most severe of all T-cell defects. You can see that severe combined immune deficiency does not represent a very big slice of the pie compared to the rest but because it is uniformly fatal it represents sort of the golden opportunity for early intervention.

Historically the presentation of SCID was associated with a baby who had a bacterial infection, a mycobacterial infection, a yeast infection as exemplified by candida, pneumocystis pneumonia or a respiratory virus. Historically the mortality rate was about 40 to 50%. This represents the pre-newborn screen era and as I said mortality in my time has been at about 50%, back in the 80s it was even higher but in the modern era I would say it has been running about 50%.

There are some non-infectious clinical presentations and I just want to mention this because they're often missed by clinicians. This is a baby, these are two different babies, but they're babies that presented with a particular manifestation of SCID called Omenn Syndrome. This is where the immune system actually starts attacking the baby even though there's not much of an immune system, there's enough that when it goes haywire it causes disease. Weirdly enough this is often misdiagnosed as milk allergy and so the babies often don't come to medical attention until they're in extremis.

Here are just a couple more pictures. You can imagine how this might be seen by a dermatologist or an allergist before ever coming to the attention of an immunologist. It's just not ... It doesn't look like something that is so immunologically mediated.

Now, I want to contrast the early historical outcomes for SCID with the current outcomes for SCID. This is an amazing study that was done by Sung-Yun Pai that compares kids who were transplanted at older than 3.5 months with active infection. That's the orange line that you see. What's on the Y axis is the probability of survival. Higher up means better survival, lower down on the graph means worse survival. You can see the orange line, meaning the babies

that were older that had active infection, they're the ones that had about a 50% mortality rate. If you compare that to the upper blue and green lines where they're diagnosed earlier and without infection their survival is much, much better. We typically, today, say that the kids who are diagnosed by newborn screen have a 95% chance of survival. You can see that's really markedly different than the pre-newborn screen era.

Why is this? It's because it's a race. When the baby gets infected with something that infection is going to relentlessly progress unless a new immune system is brought in through bone marrow transplantation. If the infection gets a head start the chance that the new immune system coming up and being able to control the infection is less whereas if you do a bone marrow transplant in the absence of infection the chance of a successful outcome is much higher. Bone marrow transplant and infection, it's always been a race. People have tried to do different things to help the new immune system come along but basically babies with SCID have no ability to eradicate infection specifically viral infections until they get a new immune system through bone marrow transplantation.

Newborn screen for SCID rests on the identification of something called a TREC. This is a little bit different than most things that are detected by newborn screening in that it's a PCR based test as opposed to mass spectroscopy. I'll explain why this works in a minute but the concept in this cartoon is that it's still taken from a blood spot but your PCR-ing for this DNA TREC circle as opposed to looking for some chemical modification.

The reason this works is if you look at the bottom of this slide here the lymphoid progenitor goes through a series of steps before it turns into a T-cell and T-cells are, of course, what's defective in SCID. In the thymus, which is the bottom rectangle, these cells go through a series of orderly developmental processes and as part of that there's actually rearrangement of the DNA and the TREC circle is a byproduct of that DNA rearrangement. Basically, when a T-cell is born in the thymus gland it has a TREC circle and if there's no T-cell that's born in the thymus there is no TREC circles. It's actually a very sensitive way to identify newly developing T-cells in the peripheral blood.

Now, in almost every state and in fact every state that I can name, once a TREC positive infant is identified the next maneuver is to perform flow cytometry. The actually work flows vary quite dramatically from state to state in terms of who does the flow cytometry, how the baby gets there but if I can just sort of average all the states together flow cytometry is almost always the next step to happen. Flow cytometry works because you're basically asking, do we find T-cells in the peripheral blood of this baby? The first screen is to look for TRECs, if those TRECs are low it implies that there's low T-cells and then the next step would be to do flow cytometry, which is just an alternative way to quantify T-cells.

As part of this evaluation we usually look at two other types of lymphocytes called B cells and natural killer cells. It can be helpful to look at those to help you understand what type of gene defect is leading to SCID and it can also help you understand a little bit whether the baby has lymphocytes that are low overall, globally or whether it's just specific for T-cells.

SCID is not the only cause of T-cell lymphopenia. T-cell lymphopenia referring to low T-cells. In fact, it's not even the most common so although newborn screening for SCID was developed to find those infants and it actually does it amazingly well there's a lot of other diagnoses that come out as a result of this screening. Probably all of you have seen on your reporting sheets that there are opportunities to identify cardiac defects, syndromes, prematurity, other types of T-cell defects so all of these can be detected as low T-cells in a newborn infant. Only a subset of the patients will actually have SCID.

This has led to a recognition of some syndromes that we didn't previously understand have low T-cells that we now recognize as having low T-cells and I've listed some of those in this slide. It's not so much of relevance for the newborn screen population but it's of relevance to clinical immunologists who are trying to sort out what the baby has.

Then, there are secondary causes of T-cell lymphopenia with cardiac anomalies being the most frequent cause. On most state report sheets that I've seen cardiac anomalies are called out as a specific diagnosis related to the low TREC. As you can see there's actually a range of things that can be associated with T-cell lymphopenia. Surprisingly neonatal leukemia is one. I was actually hard pressed to understand that until I saw my first case of neonatal leukemia and it's actually simply a dilutional affect. The baby has so many white cells that aren't T-cells the TRECs actually get diluted out by the leukemic cells.

What does a typical work up entail? I mentioned that flow cytometry is pretty uniformly the secondary screen for TREC positive infants. In all states that I'm familiar with T-cells, B cells and natural killer cells are enumerated and certainly most states mandate or at least immunologist also perform these other two markers called CD4 CD45RO or CD4 CD45RA. RA and RO T-cells are inverses. You can't be both at the same time so an RA cell is a naïve cell and an RO cell is a memory cell. The reason for doing this is that there can be quite marked expansions of T-cells but they are all memory cells, they're not newborn T-cells. There are a variety of situations where that happens. These additional markers are often utilized.

Typically most states would request that the baby be tested for HIV if not previously done and then mitogen proliferation studies are request on some state's reporting sheets. This is a functional T-cell assay that asks can the T-cells proliferate. All of this work up is really focused on identifying typical SCID, which is great. That's the population we need to identify. We need to refer them for

transplantation, absolutely appropriate. Of course, it leaves us a bit in the lurch with the kids who don't have SCID.

Not every baby with a positive screen for SCID has SCID and so what else do we do? I'll just go through this quickly. We do pay attention to the birth history because prematurity is the single most common reason for having low TRECs but infections, intrauterine growth retardation, maternal medications also are relatively frequent causes of low TREC. A good physical examination to see if there is a cardiac anomaly or complex congenital anomalies and then we also ask, could there be losses? Here the GI tract is the most frequent place where T-cells can get lost. We try and quiz the parents on the state of their stools and look for soft markers of GI loss.

As I mentioned, syndromes are the most likely category if you've eliminated prematurity. The two most common are 22q deletion syndrome, which is also known as DiGeorge syndrome or trisomy 21. These are usually screened for by just a physical exam but the features can be subtle and I just highlighted here that if your center is using exome sequencing as sort of the first screen these will not show up on whole exome sequencing. I always say you just have to take a good look at the baby. It's really ... It's not anything fancier than that.

There are a few kids who just don't really have a name. I know that the states don't like that because everyone wants an answer to the screening. I have to say there are some kids who really don't really declare themselves until later so we follow for a period of time before we declare what they're turning into. Some babies will outgrow their lymphopenia but some babies won't. I'll just make a pitch for don't delay a transplant for SCID waiting for a change. Just because you don't have a name for it doesn't mean you can't transplant it. For kids who have dramatically low T-cells even if they don't have a recognized SCID gene defect they may still benefit from transplantations.

This is a compilation from the California data, which is the best data to be published as well as an 11 state compilation that you may have read about that appeared in JAM, I think, a year and a half ago. You can just see the many different causes of having a low SCID. We do find the SCID patients by using this newborn screen methodology but we certainly find a lot of infants with other things. While that's not as important from the newborn screen perspective it does consume a lot of time and energy on the part of the immunologists following these infants.

Let me just say a word or two about transplantation. You've seen this slide before. I just want to reiterate that the absence of infection is the single best predictor of good outcome. That would be the green and the blue lines at the top compared to the orange line at the bottom. We do want to get these babies to transplant as soon as possible. At our institution we try to perform the transplant at about two months of age.

I don't want to neglect gene therapy. This has the potential to really transform the practice and the care of patients with SCID. I just want to say a couple of words about it even though it isn't mainstream yet. Gene therapy has actually been around now for over 10 years. You may have heard that the retroviral vectors were associated with leukemia. What you may not know is that the modern lentiviral vectors are safer. The infants in France that were treated with the retroviral vectors that developed leukemia they got a lot of press and I think less well publicized is the fact that lentiviral vectors are being used today. They're saving lives and they're actually very affective. I think that some day this will become the treatment of choice.

This is just a little bit of data to bring home the point that gene therapy has about an 85% success rate out of about 129 treated patients. That's roughly on par with bone marrow transplantation. That's why I can say I think this may become the treatment of choice.

There are some ongoing challenges and I'll just mention these and then give you a few vignettes. In an infant with low TREC the pre-transplant management is really ... It's so essential. A newborn with low TRECs who has absent T-cells on flow cytometry genetic confirmation of excellent SCID we would usually perform a hematopoietic stem cell transplant or bone marrow transplant at two months of age and send the baby home with restrictions to await admission. Every institution is different. Some institutions hospitalize immediately. We actually send the babies home as long as there's no potential for transmission of infection.

The home restrictions includes boiled or bottled water, no visitor, no contact with siblings, IVIGs, fluconazole, acyclovir. These are all meds to ensure that the baby shows up for transplant free of infections.

The infant presented with cough and wheezing. He was admitted and he had RSV. A transplant was performed but unfortunately this baby progressed in terms of respiratory infection and did die. This is a rarity today. We see this less than 5% of the time but it really emphasizes how critical this home management is for the places that chose to send their infants home rather than be hospitalized. This has to be nearly perfect. You have to ensure it.

There are some lessons here. Although the majority of infants with SCID do well caution in pre-transplant management must be very conscientious. Here's the problem, the families must understand that infection control has to be perfect. It's really hard for families to appreciate that. In this particular case the family of the baby that died, the mother, of course, was heartbroken. I just had a little cold. She didn't realize that a little cold was a huge event for this infant. The other thing that we often hear from a lot of families is my baby looks so normal how can anything so serious be wrong? We hear that all the time and you've probably heard it in other settings of newborn screen. It's really difficult to

communicate effectively to parents that there is something inside that's very wrong without them being able to see it.

Here's another vignette. This is an infant with low TRECs who had some post transplant adventure. This is an infant with ADA SCID and the transplantation was actually completely uneventful. There was a little mild graft vs. host. This is when the new immune system comes in and sort of recognizes the host as foreign. Was treated very successfully but the baby reactivated a virus called CMV. This is actually really typical when you treat graft vs. host. This is treated with ganciclovir and really the baby was doing incredibly well.

Here's where the adventures came in. The parents were completely illiterate. They could not write their names. They had no ability to really communicate through the written methodology so this was complicated management for anyone. The baby was on up to 10 different medications and required multiple visits. We utilized a series of pictures and verbal instructions for the family to understand what we expected of them and ultimately had a very successful outcome but it really tested our creativity to come up with something that worked for everyone.

I think this is my last little vignette here. This is an infant with low TRECs and a surprise diagnosis. The most common immune deficiency diagnosis with low TRECs, again, other than prematurity is 22q11.2 deletion syndrome. We see it all the time and we sort of shrug because these babies don't need a transplant. This particular infant in the vignette had low TRECs and was found to have a 22q deletion. As I said, we don't usually treat this with bone marrow transplantation, we usually provide supportive care and we wait for the T-cells to grow in and they generally do on their own.

But, an astute clinician noticed that the flow cytometry wasn't completely consistent with 22q deletion syndrome and on that basis sent some additional genetic testing and an additional mutation in the Artemis gene was identified meaning that in addition to having 22q deletion this baby also had bonafide severe combined immune deficiency and therefore required a transplant. This baby is now alive and well and I have to say this clinician was unbelievably astute to pick that up. I think 90% of the clinicians probably would have shrugged and said, oh, it's 22q we'll just wait it out. In this case that would have been devastatingly incorrect. Really, all credit to the clinicians who do such an amazing job trying to pay attention to every last detail with these patients can really be very consuming.

I just want to summarize this talk by saying the pre-transplant period is critical and I'm not sure we give the front line clinicians enough credit for taking care of all of those details and ensuring that everything goes right. I think another key to the pre-transplant period is getting the right diagnosis. I hope you've seen some examples of why this was really critical. Getting the right management

plan is essential. It's not one size fits all for transplant and we're still trying to figure out where gene therapy fits into the mix.

Then, I'll just end by saying it's absolutely essential to partner with the parents to get the best outcome. They need to really have some trust that you know what you're doing and in turn I think the physicians need to have great trust in the parents in order for this to happen.

I'm going to end there. I hope this was useful for you and I will turn it over to ... Actually, I'll turn it back to the moderator.

Marci Sontag: Hi, thank you so much Dr. Sullivan. That was a fantastic presentation and you're clinical vignettes really did highlight the importance of that careful clinical diagnosis and understanding the complexities of the diagnosis. Thank you very much. I always learn when I hear these and I definitely learned today so thank you.

We will now move on to Sondi Aponte. We're going to save questions until the end to make sure we have time for Sondi's presentation. Sondi Aponte is a Quality Improvement Education and Outreach Manager with the Office of Newborn Screening at the Arizona Department of Health Services. Her primary responsibilities include ensuring that newborn screening best practices are maintained through education outreach, efforts to clinical practices, hospitals and commercial labs.

Her strengths include partnership and program development and in that capacity she has been involved in APHL and with NewSTEPs for several years including the Transit Time Coin Project and more recently with NewSTEPs 360 with the aim to improve overall turnaround time at the Arizona Newborn Screening Program. She has 15 years experience as a teacher and curriculum developer and 10 years in the public health sector. Sondi holds an Associates Degree in Computer Information Technology and a post secondary teaching certificate in Computer Information Systems.

Sondi, it's *7 if you haven't already unmuted.

Sondi Aponte: I have, thank you. Can you hear me?

Marci Sontag: I can hear you great, go ahead.

Sondi Aponte: Thank you. I feel pretty humbled to be sharing this stage, as it were, with Dr. Sullivan. I'm going to try to do my best to give you a little public health perspective. Having said that, thank you again for your time. I'll be done within 30 minutes so we have time for questions.

First of all, what I want to do is just thank Ward, I think he's on the call. Ward Jacox is the PI of the SCID grant we have now and our leader and Fran Altmaier,

who many of you know, is our case manager. I also want to give a big shout out to Ruth Ann and Marcy and Yvonne and others who have really been instrumental in the work that we're doing with this project and for me personally in my career sort of as we make advancements on overall quality improvement. I just wanted to say thank you for that.

Let's jump right in. The map. You've seen the map? Did it forward?

Marci Sontag: It did not.

Sondi Aponte: Okay, so it's not forwarding?

Marci Sontag: You have to show the next slide. Are you clicking on that slide?

Sondi Aponte: Yup. Oh, wait. Slide ... I'm just clicking. There we go.

Marci Sontag: There you go.

Sondi Aponte: Got it.

Marci Sontag: Got it.

Sondi Aponte: Technology. Okay, so here it is. This is the map. Everybody has seen the map. Everybody knows the map. Really, what I wanted to say about this was that the phrase, it takes a village to raise a child, really has it's origins in an African culture where it's really common for an extended family to raise a child. It's seen as a blessing from God upon the entire community. I guess you could say, in this map, it takes a very big village, a national village, to raise a healthy child. I really think this map has been my motivation. It's on the front of my SCID grant binder and I have a huge poster of it in the office. This is what drives us and keeps us motivated to continue to work. My Culligan friend says that they don't call Arizona the 48th State for nothing. We'll ponder on that one for a minute. Anyway, this is the motivation, this is the map, everybody's who's seen it knows the map.

What I wanted to do is just take a second and talk about our beginning in Arizona. We got a slow, slow start. In 2010 and '12 it was brought up several times to the Advisory Committee. There were presentations about SCID. It was pretty slow going those first two, three, four years after the Advisory Committee had come out with the recommendation.

You could see from here, I won't go through each point, but when the opportunity came for us to apply for the grant we did that. You can see, for any of those recipients of the grant, that we have some options for which tier level we thought we would be at and where we were. We were right at the beginning. Our grant deliverables had some pieces of tier 2 and tier 3 but there were a lot of variables that were out of our control in public health and we can

talk about that for a minute. I just wanted to really say that's where we were and that's where we were coming from.

Of note, when the statute was revised it also changed the language related to testing facilities to allow for an outside lab to test. That was really new and in part, I think as a response to the lab within the lab possibility that many other states had approached and used to get SCID screening going. What we did was we just focused on what we could accomplish outside of legislative efforts on building capacity in the lab and others. I just want to shout out to [inaudible 00:27:56], her team in the lab also using the grant to build capacity, evaluating equipment, reagents, etc. It's not part of my presentation but it's certainly is part of the grant deliverables and has been working, sort of, simultaneous to what I'm going to speak about today.

In 2016 we kind of hit our stride. We were already in the second year of the APHL grant. We put together some stakeholders, started some emails trying to gauge interest and bring together a work group, if you will. We started talking with the immunologists in the state. There were only a few, a practice in Tuscon and a practice in Phoenix. We started working with some parent partners in developing champions there. It started to feel like we were making a little progress in partnership development.

That's really where we focused. I think it was great because we were able to put a lot of people together in a room who had special interest in SCID screening but in some cases really didn't know each other. It think the culmination of that was this week long series of events. I think that's really what I want to focus on today is talk about a little bit more about this SCID awareness week in Arizona. That started in ... It was in October 2016. You can see a picture of the booklet and the schedule.

I want to talk a little bit about the schedule and how that came about. It was really a regional approach. We had a conference in Flagstaff, which was northern Arizona, one in central Phoenix, one in Scottsdale, which is East Valley and in Tucson. We really wanted to bring together clinicians, parents, partners, stakeholders to bring everyone together to really sort of bring forward that momentum, if you will.

The clinical trainings were three days through the week. We brought in immunologists that would serve in that community. We brought in general practice physicians, hospitalists in some cases and had an immunologist who spoke at each one. It was great. That was the clinical trainings. I'll go ahead and talk a little bit more about that as we get through.

The clinical trainings were, as I said, immunologists, pediatricians, public health, etc. You can see from the agenda we wanted to be very consistent in our approach to the training. Regardless of whether you were in Flagstaff, in Phoenix or in Tucson we wanted to make sure that you were getting a

consistent message, that you had the same opportunity to get the resources and materials, that you really were able to get really consistent perspective and message.

The clinical trainings were also videotaped and we created an entire public health website around SCID where the presentations were posted, the toolkits, the app sheets, the fact sheets, etc. There were, in each one of the regional trainings, there were case studies on kids in that area. I think in Arizona over the last 18 months we had three late ID babies and the physicians that were in attendance and the nurse practitioners, etc. as well as public health we got to hear about those cases. I think it was really eye opening and I think, I have to say, that was one of the biggest motivating factors for physicians to come out of there and really raise their hand and say I'm ready to do whatever it takes. What do you need? I think that was really one of the great outcomes for that.

We did survey results and the survey results were uniformly very high for appreciating having the information, the toolkits. Everyone walked out of there with complete instructions on what to do to get your baby tested. All of this was sort of absent the law because we didn't have any control over what was happening legislatively in Arizona. What we were doing was focusing our grant activities around bringing people together and findings solutions to bringing awareness to SCID screening, making sure physicians were looking for SCID as part of their differential and we're meeting the sub-specialists and such that could answer questions for them and help get those kids screened and diagnosed and into treatment where appropriate. I think that was really one of the biggest benefits, I would have to say.

I've lost ... Did I lose my arrow? There we go. Okay, so at this point what I really would like to do is say I don't know how we did it exactly but we went really big and we asked for the best, the preeminent experts from the nation to keynote for us. I have to say I smile and it makes me very happy to tell you that spending three or four days with Dr. Puck and Dr. Buckley, among others, was a highlight for many of us. I'd really like to ... I think Jennifer Puck is on the phone. I'm not sure if Dr. Buckley is but could we *7 Dr. Puck so she can just share a few minutes about the highlights of the event from her perspective?

Marci Sontag: Sure, Dr. Puck, if you can, if you can hit *7 on our phone and unmute yourself so you can share your insights?

Sondi Aponte: Is she there?

Marci Sontag: I see her on the computer but I don't know which of the phone numbers is associated with hers.

Sondi Aponte: Right. Are you there Dr. Puck? Well, we can always come back to it if we need to. Dr. Buckley are you on the call? I don't know that I've seen her on the list.

Marci Sontag: I don't see her.

Sondi Aponte: Okay, all right well we can keep going. I guess what I really want to say about that was it was just amazing that we went really big and asked for the best and Dr. Puck and Dr. Buckley ... We really did this around timing. It was really serendipitous, if you will, that Dr. Buckley was already planning to come and give a Grand Rounds at Mayo Clinic and at Phoenix Children's Hospital. We virtually planned the entire week of activities around her because we knew she would be here. She agreed to extend her stay on behalf on the Immune Deficiency Foundation and that was amazing. Dr. Puck was able to work her schedule around to be here for four days to talk with providers and families and executive leadership at the lab. We just hit the road in the car for four days talking to anybody who would listen about SCID.

I just have to say I was really, really honored to have both of them there. I know it's made a significant difference and more than that they let us videotape them for the future because we really saw having educational resources available for providers ongoing would be really important and for those that weren't able to attend the conferences we wanted them to be able to hear it right from Dr. Puck and Buckley and the other statewide and local experts, which I can talk about in just a minute. We were really honored and extremely pleased that we were able to have them.

Let me go ahead and move on and talk to you a little bit about the other experts that came in to town to visit, to partner with us in this SCID awareness week. I have to say that I felt really lucky to have Heather from SCID Angles for Life, Lynn Albizo from the Immune Deficiency Foundation. When we put out the call people rallied. I don't know how to say it other than that. I think we were just a small committed group of people that really knew we had a lot of work to do. I really want to reach out to them and say thank you. It was invaluable. I think some of the other work that the Immune Deficiency Foundation was able to do advocacy-wise ... I think these are all contributors to the fact that we're where we're at today and where it looks like we're headed.

We had two meetings on a Thursday. The clinical trainings were Monday through Wednesday. We had two trainings on Thursday. They were different. The first one, which is on the left, which is the agenda that's about the partner's meeting. This was just really a non-clinical. This was for partners, public health, parents, anybody interested was welcome to come. Parents, providers and champions weigh in on SCID. I have to tell you, the feedback I got from this meeting from people that had sat in these meetings ... We typically have a monthly partner's meeting might have newborn screening advisory committee members, medical sub-specialists, neonatologist, nurse practitioners, it's a wide group of people. The feedback we got from this visit was so powerful and I have to say I think it was partly because families got up and kids were there and grandparents were there to really talk about the impact of SCID on their life. I

have to say it was, I think, really powerful for us in public health but for everyone that participated in that group.

We also had ... Just got a brief update, a clinical perspective with a few case studies. The March of Dimes was there, the Arizona Academy of Pediatrics, the Arizona Perinatal Trust, it was pretty powerful. I don't know that anybody walked out of there without, sort of, a reinforced commitment.

Then, we had a break and then we spent three hours with families, just with families and kids. We blocked out a room and we just went to a white board and we started asking parent questions. Fran helped facilitate that. She's a social worker and has 20 years experience with working with families. We were able, in a small group setting of 15 families, just talk about the impact of SCID. We asked them some of the questions that you can see. How did you learn about your diagnosis? What could have been done differently? Where did you find your resources? How are the kids doing? What would you like the next family to know? I think, again, that was so powerful.

We actually brought in a group raising special kids, which I think all of the states have something like raising special kids, to really introduce one another, to really talk about how we can put these families together as strong champions. I have to say, SCID Angels For Life was the one that introduced us to these families. They weren't well known to us in Arizona because we don't have the disorder on our panel. I think that was really, really special that we were able to make connections with families.

It was just really powerful. By the end of the week it was just, I don't know, it was just amazing. We were all spent but I think there was a lot of momentum that was really brought forward on that. As a result here are some of the early outcomes that you can see. I think better communication, we talked about that, collaboration among the groups that I mentioned as well as with the Arizona Advisory Council on Indian Healthcare. This is something new that we're moving forward on. It brought champions into the state like Lynn. We include parent partners. We value and appreciate the role that parents have in teaching us about this disorder and the impacts.

We found an AZAAP Chapter champion or pediatric champion. He went to the Phoenix training and he was so moved by it. I have to tell you, he was alarmed about that two month virus, the giving the rotavirus that he just didn't want to do it for any of his kids. I had pediatricians come up to me that whole week and called me after that said I'm going to do everything I can to rule out SCID before I give that live rotavirus. I'm not going to do it. What is it going to take? I think that was pretty amazing.

I have to say PerkinElmer Labs. They stepped up. They attended these events with us. They stepped up to provide a service to Arizona providers and families that for $18 they would run the full SCID panel. I can tell you, that has been

really coming to fruition just in the last few weeks. We can talk a little bit more about that. Two hospitals are going to start SCID screening in the next few weeks. We're helping them with flow sheets and algorithms. They're going to do that with the PerkinElmer Lab for whatever, the next period of time until our legislative efforts hopefully catch up.

There's one thing I want to say about the early outcomes. If you don't know about this or you're not watching closely, our Governor Ducey, in his State of the State address said, "Every year babies across the country are born with severe combined immunodeficiency, SCID. It's a rare genetic disorder that if not detected and treated early its deadly. A baby born in Arizona today is automatically screened for a number of diseases but not for SCID. Let's change that by adding SCID to the list. We have the power to save these precious human lives so let's act with urgency." That still gives me goosebumps. It's just been a week or two. Those are some of the early outcomes and I think it's very promising.

Really to wrap up here are some of the things that are on the agenda statewide over the next couple of months. We're pretty excited about that. There will be SCID presentations throughout the next few months. I think, on that note, I want to just really thank all of our partners, everyone that's come together to help with this. On a personal note, I didn't come to newborn screening with strong credentials or even a strong public health background so I sort of hold on to this quote by Margaret Meade to remind me that we can do something. Everyone can do something. I think it's so important, the timing, after all of the marches and everything last week that this really, really came to the forefront for me that a small group of thoughtful, committed citizens and that's what we saw in that SCID awareness week, really came together to indeed change the world, at least ... One state at a time and we believe that Arizona is going to be next. We might be on the 48th of the 50 but I think we're going to get there.

I just have to say thank you again HRSA and APHL for the opportunity with this grant. They even helped us to extend a year so that we can continue the good work. I don't think any of this would have been possible without them. I just really want to say thank you on behalf of the Department of Health for this opportunity and giving us the means and the resources so that we could continue to take on this big, powerful, important work. Thank you.

Marci Sontag: Thank you Sondi. On behalf of NewSTEPs and APHL, [inaudible 00:44:26] Public Health, we really just can't thank you enough for all of the work you've put into this and your dedication and enthusiasm to pull it all together. You have put in an incredible amount of work and it has paid off. Congratulations on everything that you have done in Arizona and for the babies in your state. Very nicely done.

Sondi Aponte: Thank you.

Marci Sontag: If anyone has questions for either of our speakers you can type them into the chat box or preferably you could hit *7 on your phone and unmute yourself and ask the question directly. In summary, I'd like to say we had maybe two of the most enthusiastic speakers in support of SCID Newborn Screening on our call. This is just a fantastic way to start the year. Thank you to both Dr. Sullivan and to Sondi Aponte for presenting for us today.

Heather Smith: This is Heather Smith with SCID Angels for Life, can you hear me.

Marci Sontag: I can. Go ahead Heather.

Heather Smith: Hi, I just wanted to comment. I was at the event in Arizona and I want to say that as a parent of two children with SCID and bringing in some of the SCID families and one of them in particular that was a late diagnosis in Arizona over the last 18 months, it was so empowering for them to be able to do and share a little bit of their story and to have their voices heard. It was just great. Sondi, they did a fantastic job. I have been involved with trying to get SCID implemented in other states before but never have I been involved in a program like that. I just really want to give them the credit that they deserve for a job well done.

Sondi Aponte: Thank you Heather.

Heather Smith: Thank you Sondi.

Sondi Aponte: It's just all of us working together but I really appreciate it. It's good to hear your voice. I'm glad you're on the call and able to share your insight.

Lynell Bizo: Thanks Heather. This is Lynell Bizo from IDF. I want to second what Heather said, it was amazing to have the families there to tell the story. I also want to thank Sondi and the whole planned week long event that brought us, Heather and I, to come out there to be able to ... We tried to leverage our time while we were there. We did our presentations and we worked with the families but we also made time and worked, as well, with March of Dimes to get meetings with the Governor's staff and share the message and really advocate while we were there. T see the outcome now is just amazing that the Governor heard our voice and it really was ... The Margaret Mead quote is so apropos because we couldn't have ... One group couldn't have done it without the other. We still have to get it to the finish line. The Governor wants it but we still got to get through the Legislature but I think it was a really great opportunity for all of us to work together.

Marci Sontag: Excellent, thank you. I think this is a model practice for future disorders that are being added to the newborn screen to engage all of the partners.

Sondi Aponte: Thanks Lynn.

Lynell Bizo: You're welcome.

Marci Sontag: Hello.

Mae Baker: Can you hear me Marci?

Marci Sontag: Yes, I can hear you.

Mae Baker: This is Mae Baker. I have a question for Dr. Sullivan. An excellent presentation, very, very ... I feel like I have studied SCID for a long time, indeed I learn new things every time she talks. My question for you is, if I heard it correctly, one of, you said, status report in terms of [inaudible 00:48:33] one of them you left, I believe, is the cardiac disorders. I just wanted to ask for more clarification is the cardiac disorders after surgery you see the lymphopenia or the disease itself? I would say the experience I see a part of it is after surgery because of the thymus getting removed. Could you comment on that?

Dr. Sullivan: Yes, thank you. That's a really great question and really practical as well. It is true that thymectomy is performed in many cases of cardiac surgery, in fact I would wager most involve removal of some or all of the thymus. That actually has a very modest effect, surprisingly, on the number of circulating T-cells. When we see low T-cell numbers in kids with cardiac disease it's not related so much to the presence or absence of the thymus because, as I said, that has a pretty modest affect on T-cell number. Most T-cells are born and leave the thymus in utero and so the repertoire, the whole T-cell compartment is largely built by the time of birth.

The reason that we see low T-cells in some severe cardiac anomalies has to do with the circulation of the T-cells. The T-cells don't just circulate in the blood stream they actually come back through lymphatics and in cardiac anomalies that circulation can be disrupted either because of pressure abnormalities in the heart or because actually the thoracic duct has been damaged or is present in an inappropriate location. We think that that's the reason that most of these patients have low T-cells, not due to removal of the thymus.

Mae Baker: Thank you. Very good. From the experience I can [inaudible 00:50:27] in Wisconsin we require NICU babies to have multiple screenings. When the kid is admitted who have anomalies to surgery they usually have a first screening and because they're in the NICU they have multiple screenings. In our experience that we see the first screening is quite normal and the second screening number is reduced quite a bit which is why I think it's very interesting to hear your comments. Thank you.

Dr. Sullivan: I think you should really publish that. I think you're probably the only group that's really paid attention to that kind of dynamic process. That would be really valuable for other people to see.

Mae Baker: Well, I do have numbers. Maybe I should do it.

Dr. Sullivan: I'm serious. I think you should. I think it would be really valuable.

Mae Baker: Okay, I'll talk to you more later.

Marci Sontag: Thank you Mae, that was a great question. Are there other questions?

Richard Hartman: Hi, this is Richard Hartman from Virginia, can you hear me?

Marci Sontag: We can hear you Richard, go ahead.

Richard Hartman: My question is for Dr. Sullivan. You mentioned in one of your vignettes a baby that had 22q11.2 deletion as well as Artemis SCID. Was the deletion a complete DiGeorge and if that were the case could you share a little bit more about the treatment. You certainly did bone marrow transplant but do you know if a thymic transplant was also performed as well as if the bone marrow transplantation was done using conditioning or non-conditioning and what about the timing of all of these particular procedures?

Dr. Sullivan: Yeah, so clearly we have an immunology ringer in the audience. The issue that Richard is eluding to is you can't really do a bone marrow transplant into someone without a thymus because that new immune system has to grow up in the thymus the same as it would in all of us. In the absence of a thymus a stem cell or a bone marrow transplant just won't work. It won't take. There's no place for the cells to grow up. The question that he raises is how did we get to the point where we could decide to do a bone marrow transplant?

You raise a great point and we angsted about that, boy, let me tell you. We spent a lot of anxious days. We decided that the most likely scenario was that this would be a partial DiGeorge and probably there was some thymic tissue there. We went ahead and proceeded. This baby did get a reduced intensity transplant but that reflects the Artemis defect not any other consideration for the transplant. Artemis is a DNA repair enzyme and so these babies are ultra sensitive to conditioning regimens that contain cross linking agents. This baby got a reduced intensity transplant and has actually done incredibly well and has engraftment that you really couldn't distinguish between any other Artemis patient that got transplanted.

We were really thrilled with the outcome. We had no way of knowing that that would be what happened. We were really just playing the odds.

Richard Hartman: Thank you.

Marci Sontag: All right, are there any other questions?

Dr. Sullivan: I'm actually going to follow up on my comments to Richard and just make the point that doing this transplant in a baby with a 22q deletion for SCID, this couldn't have been done in any other setting other than a baby detected by newborn screen, right. If the baby already had an infection we wouldn't have the luxury of just trying. The reason we were able to do this is this baby wasn't sick. That actually gives you a fair bit of luxury in the setting of transplantation so that you can try something for which you don't know for sure the outcome because as long as the baby stays uninfected SCID is not harmful to the baby, it's really just the infections that cause problems. When I say it's revolutionized the care of immunology or immune deficient patients it really has. We would never have attempted this prior to newborn screens.

Marci Sontag: I think it's hard to find a better way to end this webinar then on that note. That really just emphasizes the importance of newborn screening for SCID. Really the impact we can have beyond just those initial babies that we thought we would detect. Thank you very much to Kate Sullivan and to Sondi Aponte for presenting the complexities of the disease itself, the diagnosis, the treatment and then the implementation of screening for SCID in the public health setting and all of the different partners that need to be at the table. I think you both just did a wonderful job of being able to present the entire picture of SCID newborn screening looks like in our country.

I want to remind you all that our next call is on April 17th, a Monday, at 3 o'clock PM Eastern Time. We really welcome your topics for discussion. Those of you who are in the trenches doing SCID screening, caring for those babies who are identified following screening, if you have an idea of something you would like to present or if you have some questions and suggestions, I just don't know enough about this, please pass them on to us because we really want to make sure these webinars continue to be useful to the entire community.

Thank you so much on behalf of NewSTEPs and NBSTRN we are very much appreciative of your participation and thank you again to our speakers. Have a good afternoon everyone.