NewSTEPs

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Short Term Follow-Up Technical Assistance Webinar

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Presentations: Ofelia Gentscheff, MA, MRC, CRC, Nevada State NBS Profile

Sarah Bradley, MS, CGC, State of New York

Robin Thomas, BSN, PHN, MPA, State of California

Please direct all comments/questions pertaining to this presentation to Thalia Wood at Thalia.wood@aphl.org or 240-485-2701

Thalia Wood: Again, welcome, everybody, to this afternoon. This is Thalia Wood with APHL. We're doing our Short Term Follow Up Technical Assistance webinar this afternoon. Carol, I think we'll wait just another minute and then we'll get rolling. I'd like to know who's going to present the Nevada state profile. I wasn't sure. Is anybody from Nevada on the phone? Push star 7 to unmute your phone. Carol, I just see that Ofelia is on the phone also.

Carol Johnson: Great. Thank you.

Thalia Wood: I'm going to go ahead and go to the next slides with our presenter. Carol, why don't you go ahead and introduce us for this month? Thank you.

Carol Johnson: Thank you. Hello, everybody. Welcome to the May Short Term Follow Up webinar. We have an exciting webinar for you today. We're going to start today off with our state profile from the great state of Nevada. Ofelia Gentscheff is going to do our presentation. Ofelia's role is to provide the follow-up services to newborns in Nevada, to educate hospitals and providers about newborn screening best practices, coordinate confirmatory testing, ensure babies are referred to the appropriate specialty provider promptly, and liaison with community partners.

If she is not available, Jasmine is her backup when she is out of the office. Ofelia, if you'd go ahead and do the Nevada state profile, we're ready to listen. Thank you very much.

Ofelia G: Good afternoon. This is Ofelia Gentscheff from Nevada. On the first slide, I put together the Nevada monthly samples that we received from January to December of 2015 and the samples were for first, second, third, repeats, and diet. As you can see for January, there was a total of 5,803. February, 5,173, all the way down to December, with a grand total of 69,874 samples that we've received for the [inaudible 00:02:28].

The second slide is the statistics for 2015 of current birth, was 35,662; 6 babies died without screening, 35,044 babies were eligible for screening. The total number of infants that we screened for 2015, 35,054. There were 6 babies that were screened out of state. There were 13 babies that refused screening. The total eligible screen in-state and out-of-state was 35,050.

Now, for the last part, unknown, lots to follow up. I had a software vendor, PerkinElmer do it and it came up with this number. We're still working on the query system, so I don't think that we captured the data correctly, because this may not be accurate, but I went ahead and put it. We're still working on that.

The third slide, these were the conditions that were identified and confirmed for 2015. We had 10 for CH. Sickle cell disease was 15. FS was 6. FSD, 7. FSA is 1. Cystic fibrosis, 2. Tyrosinemia, 3 as 1. Congenital adrenal hyperplasia was 2. PKU was 2. Classic galactosemia was 1. Partial biotinidase deficiency was 1. MMA was 1. GAs, we had one baby. MCAD, 2. Then VLCAD, 1.

The fourth slide, other conditions. For the traits for the hemoglobinopathies, we had a total 1,167. For the DG Duarte variant, we had a total of 3.

The next slide, under exciting new developers, we were transitioned from the State Health Division to Nevada State Public Health Labs on January 1st of 2015. Nevada State Public Health Lab is one of five laboratories in the US and it is part of the university rather than a State Health Division. We have a newborn screening advisory committee up and running and it meets quarterly.

We received a 2-year CDC grant for the setup of SCID screening. Recently, for the first year, is for the purchase equipment or validation and staff training. For the second year, purchase additional equipment to implement statewide screening. We're looking at that suggested implementation sometime in 2017.

eReports has auto-faxing. Our vendor is working on it. Projected implementation is sometime in August of 2016. We recently got a contract from the Nellis Air Force Base, Mike O'Callaghan Medical Center in Las Vegas, Nevada to do their newborn screening testing for military families' babies. This started this month 2016.

The last slide is our contact information. I'm based in Las Vegas. I'm the only follow-up person for the state of Nevada. Jojo is the newborn screening laboratory manager based up in Reno. Stephanie Van Hooser is the Nevada State

Public Health Lab administrative director. We have our contact numbers and emails for that.

That's it for the Nevada state profile. Thank you.

Thalia Wood: Thank you, Ofelia. This is Thalia. Just a quick question. Did you have any bumps in the road trying to implement newborn screening in Nevada?

Ofelia G: Yes. We're still going through it.

Thalia Wood: We'll have a presentation about that at some other time when you think it's smoothed out. Thank you for that. Great to hear about your startup.

Ofelia G: Thank you.

Thalia Wood: Carol, if you want to introduce our next speaker.

Carol Johnson: Sure. The rest of our webinar today is going to be talking about screening for X-linked ALD or adrenoleukodystrophy. Our next speaker is Sarah Bradley. She's a genetic counselor that works in the New York State Screening Program. She also supervise a follow-up for inherited metabolic disorders, SCID, lysosomal storage disorders, and of course X-linked adrenoleukodystrophy.

Sarah, if you want to go ahead, that would be wonderful. Thank you for your help and presentation to day.

Sarah Bradley: Thank you. You'll be advancing the slides, correct?

Thalia Wood: Yes. This is Thalia. I will.

Sarah Bradley: Thank you. I'm here today to share with everybody our theory on screening for ALD in New York state. To start today, just a little bit of background first about how we do the testing in New York and some of our results so far. We'll go through our potential outcomes from screening, our diagnostic algorithm, surveillance, some considerations for treatment, case examples and long-term follow-ups. I'm going to do my best to go through the follow-up pretty quickly, but if you have any more in-depth questions, I'm happy to answer any after the presentation or my email at the end as well.

In terms of background, I'm sure by now, if you're screening for ALD or soon to be screening for ALD, you're probably familiar with this story. This little boy here is Aidan Seeger and he was a 7-year-old living in Brooklyn, New York. Unfortunately, he passed away from X-linked ALD in April of 2012. Within several months of his passing, his parents lobbied for the addition of ALD to our newborn screen here in New York.

It was submitted to our legislature in August of that year. It became a law in March of 2013 and we had until the end of that year to start screening. We did it just under wire. We started screening on December 30th of 2013. We've been screening now for almost two and a half years.

How we do this screening is we do it through three tiers. The first and second tier, we're measuring the very long chain fatty acid, C26, and we measure that twice, all the babies that have an elevated C26 on the first tier, go on to a more sensitive second tier. Any babies with an elevated C26 after the two tiers automatically are going to become a referral and called out to the geneticist, but they also go on to a third tier of testing, which is sequencing of the ABCD1 gene.

So far in New York, and this is as of last week, we have screened a little more than 600,000 specimens. From those, we have referred out 47 babies. Of those, 22 were girls, 25 were boys. We have identified 17 boys with X-linked ALD. We've also found 19 baby girl carriers. We even found a male carrier. That's a case we'll talk about a little bit later because that was an interesting one.

We've found 7 babies that have Zellweger syndrome. We've also identified a baby with a rare syndrome called Aicardi-Goutières syndrome. We have another baby who unfortunately expired, but it looks likely the baby had a peroxisomal disorder. We have one baby who's in a workup right now where it looks like the baby may potentially have a lupus, which is causing elevations in their C26.

The potential outcomes with our screen. Again, we are referring the babies out after they have elevated C26 on both the first and second tier. The possible outcomes with an elevated C26 are babies that have excellent X-linked adrenoleukodystrophy, which is obviously what we're ideally screening for. We also pick up babies who are carriers with ALD, as well as babies that have other peroxisomal biogenesis disorders.

Our referral process is the same that probably all of you do in your states. When we have a positive result, we notify the baby's pediatrician, as well as the specialty care center, and oftentimes, the hospital of birth will need to be involved as well. The baby is initially evaluated with genetics. In some of our centers, neurology does the initial evaluation and follows those babies in the long-term. We with our specialty care centers developed a diagnostic algorithm which they all follow and they have also made additional recommendations for managing these babies. We'll review those here.

With our diagnostic algorithm, the goal was really to answer the question of does this baby have ALD or does the baby have something else. The goal of the algorithm was to recommend the minimum amount of lab work or valuations that would be necessary to answer that question.

The next slide is our algorithm. You can see up on top that it's initially split into babies that have a mutation or not a mutation. I realized not all states would be

doing gene sequencing, but fortunately, we have the benefit of having that information upfront. For babies that we know who do have a mutation, we have different arms for whether the baby is a boy or a girl. Babies that don't have a mutation at that point, the fact that the baby really is not as important, but we do have evaluations to determine if the baby has another peroxisomal disorder or not.

This is just going into a little bit more detail, but for the baby boys who are identified by the screen who do have a mutation in the ABCD1 gene, when they go the specialist for their evaluation, we recommend that the specialist collects a new newborn screen sample on the baby. That helps us to confirm the DNA phasing of the gene mutation.

The recommendation from the group on the algorithm with the very long chain fatty acids be ordered at an independent lab just to confirm the finding, this is again for baby boys, and that a maternal sample be collected to see if the baby ... Again, to confirm phasing, but we also provide this feedback to the family to let them know whether the baby boy inherited this mutation from their mom or if they're de novo. We have found that about a third of the time, the babies, this is de novo, meaning that this is a new mutation and that mom does not carry it or doesn't appear to carry it.

We have performed testing for other at-risk family members. We have had baby boys who have older brothers who were born prior to the start of newborn screening, or we had one that we recently tested, an 11-year-old uncle of a baby. We will test other family members. Again, they see the genetics, neurology, and endocrinology.

The next are baby girls who have ABCD1 mutations. For these ones, we especially recommend genetic counseling. These cases, as you probably know, these girls can develop symptoms later in life, potentially. We can't say they're just a carrier. That might have implications for them and it certainly might have implications for their family. We do request confirmatory samples from the parents and the baby to be sent to us. We have in these cases identified older brothers who have ALD because their younger sisters were diagnosed or were found to be carriers.

The next is just bringing up ... It's difficult identifying these baby girls. It's a byproduct of our screening method. It's logistically very difficult for us to screen only the males. Can you imagine trying to sift through and plow only the male stuff, and when we received 1,000 to 2,000 samples every day, the logistics of that are very challenging. We do screen all babies, males and females for ALD, but then we identify baby girls who are carriers.

It also gives us an opportunity to screen them for other peroxisomal disorders. We've had baby girls who have had Zellweger syndrome and it's likely we'll find other peroxisomal disorders in the future. Again, we have also, through

screening these baby girls, identified older brothers who were at risk, but hadn't been born before our screening started. I said we performed some testing for other at-risk family members. We do not perform carrier testing though for females in the family. If there's an older sister or anything like that, we don't do that testing.

Besides carrier testing in females, the next group, our babies that are born without an ABCD1 mutation. These are babies that again have elevated C26, but no identified gene mutation. A possibility for that, maybe the baby does have ALD. If this is a boy, maybe this baby does have ALD, but has maybe a large deletion or duplication that we can't detect with our sequencing. The other possibility is that, maybe the baby has another peroxisomal disorder.

We've changed our referral process slightly for babies in this situation based on some of our earlier experiences. When we called out referrals, it's always late until we have the full information. That included the DNA information before we call these ones out. We oftentimes have the C26, the first two tier information, usually a day prior to us having the DNA information.

In instances where we know that the baby is in the NICU given the information on the filter paper, we have found that it's helpful if we call out that referral at that time rather than waiting for the DNA, because we have helped identified babies that have Zellweger syndrome who are really sick and in the NICU, and they didn't know what was going on with that baby. We provided this information and it helped point them in the direction.

Those babies, especially these really sick ones in the NICU, oftentimes don't have an ABCD1 mutation because they don't have ALD. They have something else going on. Oftentimes, if we have waited that day, it wouldn't really have provided any extra information. We've changed our protocol a little bit like that.

These babies, when they first go to see the doctor, they have very long chain fatty acids done, also plasminogen, which is another test that helps to rule in or rule out the possibility of a peroxisomal disorder. It's possible that they might need additional molecular testing, but that's at the discretion of the geneticist or the specialist that they see. So far, the diagnosis for these babies, especially the ones with Zellweger has been pretty straightforward, because once the geneticist saw the baby, if they were able to justify looking at the baby, confirm that this is what they had.

That ends the discussion of our short-term follow-up. We get back after the babies see the specialist. They all, hopefully, send us back a diagnosis form confirming what the baby's diagnosis is. In theory, they should also be sending us, hopefully, copies of the independent lab work, the very long chain fatty acids that they send. Maybe they send plasminogen and any other workouts that they sent us and we store that information. After the diagnosis was met, the specialists of course are then following the babies in the long term.

When we started screening in New York or prior to our start of screening, we had several calls with our specialists around the state to work with them and facilitate a discussion about how would these babies best be followed in the long term. Based on those discussions, we actually have a published article about our surveillance protocols, as well as the diagnostic algorithm that we received. I'll just quickly review those here.

The surveillance protocols are written for three different scenarios. One is just on the immediate, at the time of diagnosis, and then also for either asymptomatic boys during childhood and then also as these young men get older, what to do with them when they're older after the age of 18. At the time of diagnosis, it was felt to be most important from an endocrine and a neurology standpoint. Endocrine, the initial evaluations were just established care with an endocrinologist and to measure a serum ACTH and cortisol level.

We have identified one baby with who I believe at the time was maybe 4 months old. I might not be right, but very early on who did had adrenocortical insufficiency. It is important to have this done early. Neurology, entering practice at the time of diagnosis, genetic counseling. A neurologist will be an important part of the care of these kids in the long term.

For the boys who don't have any symptoms with endocrine, we just recommend regular screening of the ACTH and cortisol level beginning about at the time of diagnosis and then every 6 months thereafter, up until age 18, and then to see the doctor at least every year. With a neurology, they should be seeing the doctor a couple times in the first year and then annually thereafter. A brain MRI, everybody agreed would be helpful beginning at about age 12 months. Earlier than that is just logistically more difficult. That should be done on the frequency you're seeing here. With genetics, again, with the initial evaluation. Then from thereon, it was felt like that could be done at the discussion of the specialist, depending on each individual family.

Now, for the older boys or young men after the age of 18. Still following with endocrine is advised, but they don't need to do the blood work as frequently at this point, rather than every 6 months every year was felt to be helpful. They did need to see the endocrinologist as frequently again. It could be now every other year, and neurology as well, entering into an adult practice. A lot of times, they'll need to transition from a pediatric neurologist and following with them annually and continuing with the brain MRI annually.

Another consideration that the group have put together was just when to consider possibly referring to maybe for a stem cell transplant, which is the treatment for ALD. All of these surveillance measures are looking for early, the very earliest signs or changes in a child to indicate that their disease is starting to progress and looking for when is the right time to determine to do the stem cell transplant. That's because the stem cell transplant is only recommended during

the very earliest stages of the cerebral disease, and that's because of the high mortality rate of the stem cell transplant.

These are again some of the considerations the group had made. One of the big ones that we have found in practice is that, the MRI ideally should be read by a neurologist specializing in ALD. We have learned that there can be some, I guess, disagreement or it's not always a clear cut looking at the picture and people can interpret it differently. Finding a neurologist specializing in ALD is helpful. We've had very good luck working with Dr. Gerry Raymond and he has been very helpful working with all of our specialists and consulted with him and I'm sure he is willing to consult with others as well.

Looking at the MRI, they score it and if the severity score is greater than a particular cutoff, if it falls with a certain range, then they should consider going for the stem cell transplant. Also, if the child has a performance IQ of greater than 80, it was felt by the group that that was a good criteria for recommendation.

Next I'm just going to review a couple of cases with everybody that just highlighted some of the interesting things that you can come up with doing ALD screening. This first example is a baby girl who screened positive actually twice. She had initial sample that was a borderline sample. We requested a repeat and she had a second sample which still was elevated. Listed here are her results for the C26 from the first tier as well as the second tier.

They were elevated but just over our cutoff for both of them. The DNA results showed that she carried a mutation that had been seen in other confirmed cases of disease. She came in and saw the geneticist and we requested confirmatory samples from here and as well as from her parents. Her mom was found to be a carrier of that same mutation. When the geneticist met with the family, they learned that mom had an older son who was born in 2011 prior to the start of screening for ALD in New York. We offered to test him and unfortunately he has the same mutation as well.

He was identified over a year ago and he was not symptomatic, which was good. This is highlighting that through screening by adding this new disorder and screening for it. We're now catching kids that were born before the screen. It just adds a little layer of complexity. Hopefully, by having his sister identified, it's going to end up helping this boy, because again he can start screening and he doesn't have any symptoms or early signs of the disease yet.

Our next case is a baby boy who also had a previous borderline sample and we requested a repeat. The second sample came back with elevations on both the first and second tier, again, not very big elevations. The baby was found to be heterozygous. For everyone, it was significant. The fact that the baby has heterozygous and a boy was a little confusing. Our DNA lab at first was scratching their heads on that one.

The baby went in and saw the geneticist and they did some further testing. They did a karyotype for the baby and it showed that the baby, his karyotype was 47, XXY, which means he has Klinefelter syndrome. Typically, individuals have two sex chromosomes. Boys have an X and a Y and girls have two Xs. He has an extra X. He is a male carrier of ALD. So far, he's clinically been doing well.

Just an interesting example that we have come across. All this theoretical examples like, "This could happen. This could happen," eventually, they will happen to us. Just wanted to put that out there.

The last time that we're working here with New York is long-term follow-up. This was an ongoing process for us. Obviously, these are babies that are not going to, in many circumstances, show any symptoms of disease for many years and we want to know what's going to happen to them in the long term.

We worked with our group of specialists. This effort, I should say, was totally led by Beth Vogel here, who I'm sure you are familiar with, but working with our specialists to determine data elements. They've come up with 40 data elements that include general elements and then also endocrinology, neurology, family history, and prenatal history. Currently, it's at the point where our specialty care centers are now working with their IRBs to gain approval. This is very much a work in progress for us, but we are working in the direction of having this set up. Hopefully, we will have that done or at least more established in the coming months.

After that, just some acknowledgements. Most especially, and I failed to list her here, but it's definitely Beth Vogel, who's done a huge amount of work on ALD screening here in New York. Dr. Gerry Raymond is our expert on ALD who has been very helpful with us in New York. Others here are the specialists from the treatment centers who worked with us to create these guidelines and for what they've done.

My contact information is here. If you have any questions, I'm happy to answer anything. That's it. Thank you.

Carol Johnson: That was very excellent, Sarah. Thank you so much for your presentation.

Thalia Wood: Carol, did you want to pull questions in? I already have two in the chat box. Did you just want to wait for the last presentation or you want me to ask them now?

Carol Johnson: Sure. Let's do that. I'll go ahead then. We have one more speaker for today. Our last speaker of the day is Robin Thomas. She's the nurse consultant specialist for the California Newborn Screening Program. She works in the Clinical Services Branch and is the program liaison for the seven Area Service Centers. She's been the program lead on several newborn screening informatics projects as well.

Robin, if you would like to tell us what's going on in California with ALD, we would love to hear your presentation. Thank you.

Robin Thomas: Good afternoon. This is Robin. I'd like to thank New York, first of all, for sharing their information and protocols with us. In California, we have not started to screen yet for ALD, but we are preparing to. As you can see on the slide, we had a similar bill that was introduced in 2014 and it was signed into law by Governor Jerry Brown in September of 2014, which stated that the department shall expand newborn screening to include ALD as soon as ALD was adopted and added to RUSP.

Actually, we started earlier in California, in April of 2015 to get prepared for ALD, because we expected it was going to be added to the RUSP at some point in time. We started working early in 2015 and started preparing our computer system and our plan for how we would screen the babies for ALD.

Our plan is to start screening by July of 2016. That's our plan. Once we have our computer systems and labs in sync, we will retroactively go back to start screening babies that were screened after February 16th, 2016, because that was the day that it was added to the RUSP. At this point, we don't have any plans to add NBS 1 yet to our panel.

What you see here our flow chart, how our screening will go with ALD. I'll start at the top left. The top blue part is basically our short-term follow-up plan, and then the yellow at the bottom is the referrals once we send it out to the special care centers. If you look at the very top on the left, we'll be doing MS/MS for C26 as our tier one screen. We screen about 500,000 babies a year.

Our second tier will be the C26 and the HPLC. We're anticipating that we will have 9,000. Based on the numbers we received from New York and based on our numbers, we're anticipating about 9,000 cases a year going to the tier two. We will also do the sequencing of the ABCD1 gene as part of our newborn screening program. That's our tier three screening. Once we have the results of our sequencing, then we will refer the positives onto the Area Service Centers to create their headline cases, and that starts the follow-up with the family providers and the referrals to the special care centers.

In California, we have decided to start our follow-up with the metabolic centers. Last year, we had a meeting with some of our specialty care doctors. We have some of the metabolic neurology and endocrine doctors in the room, and discussed our plan to start screening for ALD. At that time, they were in agreement that it would be okay to start at the metabolic centers. That is our plan in California.

We also have another meeting coming up next month where we're going to reconvene some of the specialty care doctors to start working on the actual protocol. Basically, as you go back to that other slide, the same slide, once we

have the ABCD1 gene sequencing done, they will get referred to the specialty care centers and we anticipate. If it's a positive mutation, they will go to the right. If it's a negative, they will go to the left for the specialty care centers to work the babies out for any of the other possible disorders that are not ALD, but may indeed need to be followed up and the baby is maybe sick.

Once these specialty care centers do their work up, we will get a referral back. Not a referral, but they will start their reporting, which starts our long-term follow-up of the cases. You can go to the next slide.

Just a reminder here. In California, we're split by our Area Service Centers that do our follow-up. We have seven Area Service Centers, two are Kaiser and five are geographically based, and they're color-coded. You can see Kaiser North and Kaiser South is split by that one diagonal line. They go straight across the state. The next slide.

Our laboratories in California. We had a laboratory consolidation in 2015, so we went from five geographical labs down to three, and we have two Kaiser, one northern Kaiser and one southern Kaiser lab. Just to remind people of how we're split up. You can see the little red dot is where we're located. It's our genetic disease lab. We're located here in Richmond, California. For the ALD, until we actually have the approved kit for the ALD testing, most of the specimens will come here to our GDL lab for testing. Next slide.

This is just to show all of the partners that have been involved in planning for ALD. We've brought in quite a few specialty partners and there's a lot of additional communication that still needs to happen. If you can ago to the next slide.

Basically, here, we're starting with the metabolic centers and our plan is to refer. In California, our special care centers, metabolic, they're multidisciplinary. They're often endocrine and neurology interfaced within those centers. If the baby becomes positive or has symptoms of endocrine, we are trying to set our system up so that we can refer the case and transfer the case to endocrine center if the baby needs, primarily, endocrine follow-up.

In California, we don't have neurology special care centers yet. We have a lot of neurologists. Here, there's some talk about specialty centers being developed in California. If they're preliminaries, they can be referred to the neurology centers, if not to some of the panel of neurologists that we work with. Next slide.

Basically, we're talking with all of these different specialties. We're also including a bone marrow transplant center, because we know that many of these babies, if they become symptomatic, they will need to get to a transplant center right away. Oftentimes, those centers become the primary center for specialty care at the time that they're involved with the transplant.

We've developed our computer system and that's SIS, the Screening Information System program, our computer system, to add for the short-term and the long-term follow-up. Now, we're starting to work on our care guidelines. Our model I think is going to look a little different than New York's model, but we have looked at their model and probably will incorporate quite a few features of it. We're anticipating some more discussion with our specialty care doctors to help us with those guidelines.

This slide shows one of the metabolic center screens that's in our computer system. Basically, it shows what the metabolic center will see when they look at their screen. You can see on the far right, the one that has green at the top, shows a referral for a baby without a mutation. At the bottom, it has a baby that has a mutation.

It's hard to see, but basically this is their landing place and we've made some changes to our computer system so that each center can see basically what they have, the patients they have that are assigned, who's pending, who's resolved, who are we waiting for them to do their annual reports, and also the fee monitoring cases. It's going to give them now a one-shot glance at all of their cases and they can click on each sections to get their case list. Next screen.

There's a picture of ALD service report, which is very hard to see, but Lisa wanted to see what's the long-term follow-up plan was. This picture is really hard to see, but I'll just tell you briefly.

There are sections that show the case resolution, the follow-up status of the baby, what the disorder was diagnosed as, also the date they made the diagnosis, when they made contact with the patients, which specialists are involved in providing services for the baby, which confirmatory tests they've done, any additional tests they've ordered, interventions that are planned, medical treatments, and the status of the clinical findings of the baby, any significant health problems also when they have their appointments, and information like if the baby passed away, what is the cause of death and the date of death.

There are some screens that we're anticipating building out for the MRI follow-up. For the frequency of the MRIs, we haven't established a timeline yet, but we've built the infrastructure in our computer system to allow for the frequent monitoring and results of MRI testing. That's pretty much in the long-term follow-up screen.

Thalia Wood: Robin, this is Thalia. Is it okay if I send the PDF that had that hard to resize to the attendees of this conference?

Robin Thomas: Absolutely.

Thalia Wood: I will send that out when I send out the surveys to everyone. Before I turn this back over to you, Carol, I'm going to go ahead and ask some of the questions that were in the chat box. It looks like so far there's three questions all for Sarah. Sarah, make sure your phone is unmuted. Sarah, you flagged 47 cases and they all had something, either confirmed or carrier status. Were none of these false positives?

Sarah Bradley: Sorry. I'm just pulling up that slide. Can you hear me okay?

Thalia Wood: Yes.

Sarah Bradley: Good. I'm sorry. Say that again. You said 47 referrals.

Thalia Wood: Cases. They all had something, either confirmed or carrier status. Were none of them false positives?

Sarah Bradley: At this point, there is one baby that is in the workup. It doesn't appear so is the short answer, with one caveat, that we do have one baby that was a boy who had an evaluated C26 but no mutation. The baby had very long chain fatty acid and plasminogen done. The plasminogen was normal, but the C26 was still elevated, an outside of lab. That baby is undergoing workup. They're ordering deletion duplication testing to make sure he doesn't have an ABCD1 mutation.

They have a running theory though that actually he has a congenital lupus and his mom has it as well. Their theory was that maybe it was due to that. His workup is still continuing. There's one we don't know about. So far, other than him, we don't have other false positives.

Thalia Wood: Thank you. Stay on the line. I have a couple more questions for you. What type of time frame is New York state finding from, number one, collection-to-result sequencing, and, two, receipt at lab to the first, second-tier testing? That's just the first part of the question, and then there's more.

Sarah Bradley: For the receipt to the lab, all of it is done off of the baby's initial screen, if that's what the question is. Tier one, two, and three are all done off of the initial specimen. In terms of the turnaround time, we usually get the first and second tier done within, I'm going to say, about 3 days and then it goes on for DNA testing. That can be about a day, but we have had cases that has been more complicated or there was a structure to failure or the interpretation was difficult and that may have taken an extra day, so it could take up to about 5 days. This is from what we received, a specimen here.

That's a ballpark figure. We tend to think that these ones are maybe a little less time-sensitive than some of our other conditions. It's not like a galactosemia. If these could have ALD, they're not going to become symptomatic most likely for several years. There are some times where they take the extra afternoon to

make so get the DNA interpretation, feel comfortable about that before reporting that.

Thalia Wood: Thank you. The next part of that question is, "Are families notified that sequencing is being performed or is it just the NICU population?"

Sarah Bradley: We've performed the sequencing on anybody who has a positive result after the first or second tier regardless of if the baby is in the NICU or not. The families, when there's a positive result, they're given that information by the specialist.

Thalia Wood: Can you let the audience know what the cost per child is for the program also? What was your budget to bring these on?

Sarah Bradley: That is an excellent question and I don't know that information off the top of my head. I could find that out. I don't know if Beth is on the line, if you might know that information, Beth. Sorry, it's not something I know off the top of my head. We got one-time appropriation to get the testing up and running, and that was to buy it. I know that was $100,000, but I don't know what the exact ongoing cost per baby is, but that's something we could find out.

Thalia Wood: Thank you for that. A question that goes along with that for Sarah is, how are you paying for your long-term surveillance?

Sarah Bradley: The long-term surveillance, and that's something that Beth could speak to about a little bit more, we don't have specific funding for it. We have talked about different models about how we might structure this. Currently, we don't have a means of reimbursing the specialty care centers to do data entry or how that's going to work. We have talked with them about the possibility of us sending a staff member, probably Beth or myself, to them to help them pull this information and enter it into the database. That, we don't have separate funding for.

Thalia Wood: The next question is for Robin. Is the cost for your planning long-term follow-up included in your newborn screening fee? If not, how do you pay for it?

Robin Thomas: The short answer is yes. All of our fees for follow-up and everything is included in our newborn screening fee. We are anticipating a fee increase to add ALD and the costing is still under way. We don't know exactly how much we're going to increase our fee, but there will be an increase.

Thalia Wood: Next question, I believe, must be that for Sarah. For those babies identified during your first year of screening, what has been the compliance of the long-term follow-up lab testing and clinic visit?

Sarah Bradley: That's a great question and some of it we're still determining if we followed those ones, because especially babies identified early on have gone for one MRI, maybe two at this point. I guess I'm going to say we don't know at this point. The

specialty care centers were in pretty regular contact with them and we haven't heard of any major compliance issues from them and they're forthcoming with that information.

As we start going into long-term follow-up more and collecting that data, I think we're going to have a better sense of that. I haven't heard of any outright problems with that at this point, but obviously that will be a problem most likely going on in the future, and then we'll have a better sense of it going forward as we continue to move down the long-term follow-up path.

Thalia Wood: Great. Thank you. That was all the questions in the chat box. If anyone else has any questions, we'll take a few more minutes here. Just do star 7 to unmute your phone or type one into the chat box and I can relay it the presenters.

We're not hearing any more questions. I'm not seeing any more appear in the chat box. Carol, would you like to wrap this up for us?

Carol Johnson: Sure. Just wanted to remind you all that there will be a short survey that will be sent out to get some feedback from today's webinar. Also, please contact Thalia if you have any ideas for future calls or any other feedback you'd like to give us. Last but certainly not least, I'd like to thank all three of our presenters. Thank you so very much, Nevada. That was interesting. I think Thalia is right. We're going to want to hear more about your transition in the future, I think.

Thank you again to New York and California for all the great work that you're doing on screening for X-linked ALD. Great work and keep it up. We'll be in touch I think with you later to hear how it's going in the future. Good luck. Good luck to California and your implementation.

Thalia Wood: Thank you everyone. Thank you for joining us, everyone. We'll have another webinar in July.