CF QI Timeliness Webinar
IRT/IRT/DNA in 2-panel States
October 18, 2017

Marci Sontag: All right, let's go ahead and get started. Welcome everyone to the bimonthly cystic fibrosis newborn screening timeliness webinar. We are very excited to have you all on the call today. The purpose of this call is really meant to be very interactive. We would love to have a call that allows programs who are ... typically the audience for today's call is going to be the states who are two screen states, either two mandated screens or two regularly collected screens, to allow them to discuss their current experiences with their two screens, specifically most of these programs using IRT, IRT-DNA, or moving towards IRT, IRT-DNA.

Let me just give you a little background first, and then I'm really going to hand it over to newer screening programs who are using those algorithms so we can hear their experiences. In background, cystic fibrosis newborn screening has been universally adopted in the United States since 2009. However, there really are varied outcomes in the time of intervention, time of diagnosis for across each of these states. A lot of that is related to newborn screening algorithms within those states. States with two newborns with two routine newborn screens have additional challenges in the timeliness for CF newborn screening as those results aren't getting called out until the second newborn screening. However, there are many solutions that have been put into place across these states to help with that timely identification of at risk infants.

The overview for today is that states with two routine screens or implementing or evaluating IRT, IRT-DNA will discuss their approaches and their outcomes within their newborn screening programs. These are the questions that we asked of each program. The questions were related to the number of birth at the timing of screening, their details of their algorithm, what are they doing related to each of these activities? What are their cutoffs? What DNA palette are you using? What of their timing? Then outcomes if available. Do they have the age of call out of abnormal results, the age of intervention, and the age of diagnosis?

I was going to start with the state of Texas, and Dr. Rachel Lee has agreed to go first as long as her microphone will work. Let's see if her microphone works. Rachel, I cannot hear you. I'm going to try to redo it, but that's not working, so let me look if I can see on the ... why we might not be seeing you, or hearing you that is. Rachel, it looks like you might not have a microphone on your computer. It looks like Rachel might be trying to call in. Rachel, when you call in, if you could enter your participant code.

While Rachel is doing that, I'd like to move on to Colorado. We'll give Rachel just a minute. Is that okay, Rachel?

Dr. Rachel Lee: Can you hear me now?

Marci Sontag: Oh, we can hear you now.

Dr. Rachel Lee: Okay, I'm using the phone, although against your recommendation I'm using the phone. I hope that's okay.

Marci Sontag: It is okay, I'm so glad it worked. It's working perfectly. Thank you, Rachel. Do you want to share your slide or would you like me to share your slides?

Dr. Rachel Lee: Can you share my slides? That will be fantastic if you can do that.

Marci Sontag: I would be delighted to, give me just one second. Have to find that, where I had your slides. Okay, Texas. Thank you all for your patience. My computer's a little slow this morning, Rachel, I apologize.

Dr. Rachel Lee: That's okay. I just want to double check, you just want me to go through the questions you had sent in to us, correct?

Marci Sontag: You can go through the questions, and then if you have other additional details, you don't have to just read through that list of questions. Please feel free to tell us your experience with using this, other things that you think might be helpful for states that are about to implement or thinking of implementing this, and states that are currently implementing that might want additional information. We really want this to be discussion based, so I'm sharing Rachel's slide, and then if all of you would like to after Rachel gets finished, you can feel free to ask questions as well.

All right, Rachel. Take it away.

Dr. Rachel Lee: Okay. Well, it says on the slide, in Texas we use the IRT, IRT-DNA algorithm because we are a two screen state. We started screening back in 2009, we've been doing it for almost eight years, and we are a big state with a large number of births, about 400,000 annually. Since we're a two screen state, but we don't receive two screens for every single one of the babies, so our approximate number of all of it, it's 780,000 a year.

For two screening, because we collect the first screen recommendation it's 24 to 48 hours, and for the second screen the recommended timeframe is 7 to 14 days. When we receive the first screen we test them for IRT first, and if the IRT is elevated, and we would put out as indeterminate. Then asking them to send on the repeat screening, and when we receive the second screen we test them for IRT again. The cutoff for the IRT is 60 nanogram per mil for infants that were collected at less than 21 days of age. If the baby's a little bit older when the specimen was collected, that is like 21 days or older, the cutoff is lower, about 46 and 45 nanogram per mil for IRT.

We use the Luminex 60 mutation panel, and the cost it says there. This is just approximate cost, including the reagents, equipment, the maintenance, and personnel. I think that's it for that, for this approximate number of cost, and assigned to any indirect cost. For IRT it's about $3 a specimen, and for DNA it's about $75 a specimen. Do we do all seconds for IRT? Yes we do, and we don't check their first screen results, we just go ahead and test them for all IRTs. If the second screen were tested with positive or elevated IRT, they'll refer it to DNA automatically. We do not refer any, request any first screening to DNA automatically. We do sometimes receive special requests from these centers suspecting that the baby may have cystic fibrosis, and they will request us to just pull the first screen out and test it right away for the DNA, and we do that upon special request.

Addition, do we have an extra ultra high cutoff? Yes we do, we have an IRT, if they are more than 150 nanogram per mil, and even with no mutation identified we'll still recommend for testing. I think so far we have identified six cases this way. Do we have a protocol to testing on the first screen if second's not available or it's not matched? Yes, we do. If the first screen's elevated, and no second screen specimen is received by 30 days of age, the first screen's automatically reflects to the CF DNA. Usually it's about 20% of first screen with elevated IRT actually gets reflects to DNA, and we have identified I think more than 30 CF cases this way.

Outcome and seeing as it is IRT, IRT-DNA, we usually do not report out abnormal results until the second screen is elevated, and the CF DNA testing completed. The median age of reporting presumptive positive results is 22 days. At the other, you may not see, and I don't know if you can see on the slide or not, by the end that the median age of diagnosis is approximately 30 days for the state of Texas.

That's all I have.

Marci Sontag: Thank you so much, Rachel. Quick question about that age of diagnosis. Is that with the confirmed sweat test? Are you waiting, that each of those babies has a sweat test and that's the median age of diagnosis with the sweat test?

Dr. Rachel Lee: Yes, we do recommend sweat testing right away, and they usually schedule and are able to get the result to us, and with diagnosis as well.

Marci Sontag: Excellent, so your program collects that sweat test value within the follow up.

Dr. Rachel Lee: We collect if sweat testing is done, yes.

Marci Sontag: Okay. Okay. I had another question about your program, but I'm not remembering it, so let's go open it up. Do others have questions specifically for the Texas program before we move on?

One thing I noted of your program that I think is different from many of us is that you are identifying kids with that ultra high IRT algorithm. I think many programs have started to move away from that ultra high IRT because it was just, they weren't identifying to the positive predictive value was essentially zero, because you weren't identifying anyone in that. I'm glad to hear that you identified some, and you have enough babies to make that work, but with an ethnic distribution I suspect that might require.

Dr. Rachel Lee: Yep. Yeah, we review, because I'm sure all programs do, they review our data annually at least. We've been thinking that is it still worthwhile for us to continue doing this? For now it's still yes, and of course we have consulted with our pulmonologist as well. The other thing that we do is that we do test for all second screens. We have, because some babies we realize that they never had a first screen done. They may have a second screen only or the first screen may be unsatisfactory, so we found it easier for us to just go ahead and test all second screens. We have identified a few cases, I don't remember the exact number, that had a second screen abnormal but first screen maybe it's normal, or actually not in sets, or not collected.

Marci Sontag: Right. Yeah, that is another thing, I think many of the states doing two screens only test IRT on that second specimen if they have a positive first IRT. Again, that's something that appears to be paying off in Texas.

Dr. Rachel Lee: Yeah, it's like mass production here, so it's very hard for us to customize for any specimens, saying, "This one doesn't do IRT, this one does." It's basically easier for us to do it this way as well.

Marci Sontag: Yeah, yeah. I will let, I know some of the other states that are doing that can comment on how they are doing that matching and sorting those out, because I know Colorado's doing that. We will let Mark address that in just a minute. Question that was just asked, do any state follow up programs call out one mutation for providers for quicker intervention or only two mutations? I'm going to let Rachel add to that first, and then as we get to each state we'll remember to ask each state that question. That's a good question, Kristin.

Dr. Rachel Lee: It is a great question, and it really depends on your mutation panel, or are you doing sequencing and whatnot. Because we are only doing a 60 mutation panel, we do not think it's sufficient enough to cover our population with all CF diagnosis. We are following up with one and two mutations cases.

Marci Sontag: Okay. All right, does anyone else have additional questions for Texas? Rachel, stay on your phone, because we might come back and have questions for you in a little bit.

Dr. Rachel Lee: Sure.

Marci Sontag: Okay, I am going to pull up the Colorado presentation next, and Stacey Martiniano's. Dr. Stacey Martiniano from our CF Center here in Colorado as well as Mark Dymerski.

I apologize, Rachel, I didn't introduce you properly, I just kind of threw it to you because, you know, who needs an introduction to Rachel Lee? Rachel, would you mind going back and just telling us who you are for those of you who might not know your role?

Dr. Rachel Lee: Absolutely. I am Rachel Lee, and I'm from Texas, and I am the manager in the biochemistry and genetics branch. This branch includes newborn screening as well as clinical chemistry. I've been with newborn screening since 2005, I think, so it's been a while, 12 years.

Marci Sontag: Great. Thank you, Rachel. Now Stacey, I'm going to hand it to you. I think you might be sharing your presentation with Mark as well, so I'll let you introduce yourself first and anyone else on the team that's going to be presenting.

Dr. Martiniano: Great, thank you. Can you hear me?

Marci Sontag: I can hear you.

Dr. Martiniano: Oh, good. I'm Stacey Martiniano, I'm a pediatric pulmonologist at Children's Hospital of Colorado and the University of Colorado. We put our data together, kind of summarizing, we focused on the last year of our newborn screening from July to June. Darren Michael, the newborn screen program manager at the date lab as well as Mark Dymerski and Greg Bond helped with this data, and they work for the Colorado Department of Public Health and Environment, and work in the newborn screen lab. Thanks to them for helping, and Mark, please feel free to help if I say anything wrong.

All right. Do I have control of this slide? Probably not. Oh, look at that, there you go. In the last year we had about 65,000 births in Colorado. Our state lab also performs newborn screening for Wyoming, and their estimated birthrate was 6,400 births per year. Also our state lab has some small contracts with some Arizona hospitals, but this is primarily and we'll focus on Colorado and Wyoming for now, for today.

Here are the details of our IRT, IRT-DNA algorithm. Similarly, we perform the first screen between 24 and 48 hours of life, this is primarily done in the newborn nursery. Then the second screen is done between 8 and 14 days of life at the PCP's office. We have two screens for not just the CF newborn screen test, so other screens, and so in our situation we only perform IRT testing on a second screen if the first screen was elevated. Our IRT cutoffs, our first screen IRT cutoff is 60, and that's fixed, and same thing, second screen is an IRT cutoff of 60 at fixed. Like I said, we only perform that second screen if the first is greater than 60, and we have a match system that is in place. Then for our DNA,

we're using the Luminex 39 mutation panel. We perform that in house currently about once weekly.

Some additional algorithm details regarding some of the questions Marci asked us to look at. We do have algorithms that would include DNA that we would perform on the first specimen if we had a first IRT greater than 40. We implemented that about a year to two years ago, and we have detected CF patients with this algorithm in place at an earlier median age of life. We also have, we perform DNA off the first specimen if the second specimen is not received or if we are unable to make that match. Typically the lab starts looking for missing second specimens sometime between two and four weeks since the date of birth.

Then, additionally we have a mechanism that we as CF providers can make special requests for DNA to be performed off the first specimen. For example, if we have a CF sibling born, if we have a baby in the NICU that we know of with a codename alias that we want to kind of speed the diagnosis or perform the DNA testing even if the first IRT is low, or if we had some other clinical indication. If a pediatrician were to call us and were concerned about CF, we may consider asking for DNA performance on the first specimen.

Then we also do have an ultra high cutoff that would result in sweat testing if no mutations were identified. In our situation we have it that if we have an ultra high IRT greater than 150 on the second specimen and zero mutations, or in the case where we did not have a second specimen available and that results from the first IRT were greater than 150 and zero mutations were identified, we recommend sweat testing. Then I will make a note that our current practice is that our state lab does call out single mutations to the pediatricians to recommend the sweat test in order to hopefully facilitate that quicker. If there's two mutations, they call those out straight to us as the CF Center in the state, and then we help facilitate getting that patient in same day or the next day.

Here our cost estimate, our IRT cost is about $2.25 per sample, and that is the estimated cost for the kit and personnel, but not necessarily the equipment or the reagents, we're on like a rental sounds like system for that. Then the CF DNA is $220 per sample, and that does include the cost of the equipment, because we do own the equipment with a seven year depreciation estimate value. Here are our outcomes for the last year, we had 11 CF diagnoses in Colorado and Wyoming combined, plus one CRMS diagnosis. In this we did have one false negative in that last year. Our median age range for state lab call out to us with the CF results, either two positives or one positive mutation was 21 days, with a range of 6 to 35. The median age of presumptive diagnosis where we saw them in the office and started treatment initiation was 22 days, so basically the next day.

In Colorado, we have a practice of if we have a presumed diagnosis and we have started therapy, we often wait a little bit for the confirmatory diagnosis with the sweat test in patients we know have two CF mutations. Our median age of a

confirmatory diagnosis with sweat test was 60 days for that last year with those 11 CF patients. That's it.

Marci Sontag: Great. What questions to people have for Colorado? Mark, I was going to look at you for a minute. If you don't mind commenting on how Colorado does the matching. Stacey mentioned that, that we're only testing the second screens if the first screen is positive. Do you mind talking about how that happens?

Mark Dymerski: Sure. The samples are compared, we do a thing called linking where first and seconds are matched, and then the samples that don't compare are analyzed as if they were first screens.

Marci Sontag: Okay, thank you. Any questions for Colorado?

Dr. Rachel Lee: It's Rachel, can I ask a question?

Marci Sontag: Of course.

Dr. Rachel Lee: Okay, how did you guys determine, I see that you said you just implement the first screen that if it has the IRT more than 140, and you reflect to CF DNA right away. How did you determine that number, 140?

Dr. Martiniano: We have looked at the CF diagnoses for the past I think three years, and just kind of looked at their first IRT, and determined just within our population if there was a cutoff that would have had more of a higher positive predictive value and less false positives. We came up with the 140 based on our patients. I don't remember the exact numbers, how many we would have caught or missed, but the goal is that we could at least pick up at least half of our patients early, within that first week of life, to try to move our age of diagnosis earlier. Historically, our median age of diagnosis was 28 days, and so I think this has helped us get those more likely cases earlier.

Dr. Rachel Lee: Got it. That sounds great, that we've been considering to do that as well. The question, of course when we do IRT, IRT-DNA, that one of the intentions is to hoping that computing IRT-DNA, we're hoping to reduce false positives and also reduce the number of carriers that identifies. I'm wondering by doing this, automatically reflect first screen, do you see any increase in false positives or increase in the number of carriers that you identified?

Dr. Martiniano: That's a good question, I don't have the exact numbers, but we have not had a significant increase in carriers I can say. We also have less births, so I think that comes more carriers.

Marci Sontag: I sat in on the meeting when you were all deciding to move that.

Dr. Martiniano: Yeah.

Marci Sontag: At that 140 cutoff, and I know looking retrospectively, I think you said you might identify one or two more carriers per year given the historical data. It would be interesting, and Mark in virtually looking into that maybe we could pull that data out, because I think that's important. How many additional carriers are we finding by moving things around a little bit?

Dr. Martiniano: Yeah, for this project I just pulled the cases, but really looking at our carriers is gonna be great.

Marci Sontag: Yeah.

Dr. Rachel Lee: Thank you.

Marci Sontag: Oh, go ahead, Rachel. Do you have another question?

Dr. Rachel Lee: No, no, I was just, thank you.

Marci Sontag: We have a couple questions from Lani. Lani Culley is from Washington, and they are currently evaluating what they are going to do. They've kind of been data gathering on what algorithm to be using and to maybe switching their algorithm, because they're also a two screen state currently doing a modification of IRT, IRT. Lani asked, for Texas what is your ratio of CF cases to CRMS cases with your algorithm? Do you know how many CRMS cases you've identified recently?

Dr. Rachel Lee: I think it's almost, okay, I can double check. We don't, unfortunately we did not collect CRMS data right away. We kind of put them all together in one pot. We just started separating them recently, so the number we have is almost like 10 to 1. We have 10 CF cases to 1 CRMS cases. I don't think that is very accurate number because of how we collect data initially, unfortunately.

Marci Sontag: I think that's true for many states, is that it's hard to collect that data and really get a true accurate estimate of the CRMS cases. Yeah, I agree.

Lani also asks for all states, how has your timeliness and sensitivity changed since switching to IRT, IRT-DNA? I'm gonna answer for Texas because Texas started out with IRT, IRT-DNA, so there was no sensitivity expressed that was even compared to. Stacey, do you want to answer for Colorado? If not, I can be your backup if you want.

Dr. Martiniano: I'll count on my lifeline, Marci. You help me with this. Switch experience, yep.

Marci Sontag: Yeah. Our sensitivity has improved dramatically since moving to IRT, IRT-DNA, and what we could show you is that had we not switched, because what we did when we switched from IRT-IRT to IRT, IRT-DNA, we lowered our first cutoff dramatically from 105 down to 60. That's where we caught those kids that were being missed. We would have had about an 80% sensitivity had we not moved

there in that same timeframe. We would have had about 80% sensitivity had we not moved that cutoff down to 60, versus now we have over 95% sensitivity. Really a dramatic difference.

Dr. Martiniano: You attribute a lot of that, though, to reducing our cutoff though too, right?

Marci Sontag: Yeah, I think that it's entirely due to reducing our cutoff. We were able to be more specific with when we added the DNA, so that allowed us to reduce our cutoff, but really it's that reduced cutoff for IRT that has impacted that sensitivity. It's still the kids that we're missing, I don't know about that last false negative, but in general the kids that we're missing in Colorado are still related to IRT cutoffs being just below our cutoff versus there being risk on the mutation panel. Stacey, is that still true?

Dr. Martiniano: Yes, so we had in this case that last year, and he had bowel issues, but his IRT was 29. Then, but not in a codename alias, but still some abnormalities. Then just this year we just had one, the IRT was 55.

Marci Sontag: Okay.

Dr. Martiniano: Just missing, just barely in that one.

Marci Sontag: All right, not hearing any further questions right now for Colorado or Texas. I'd like to have Utah go, and I see Kim and Andy there I think, and I think Fadi may have had to leave. I'm not sure, but Kim and Andy, I'll let you guys take it over. We're not hearing you, it looks like you went on mute, but I'm still not hearing you.

Maybe, I think I see you, Andy, through the computer screen, and I see it looks like you're talking, and it says it's unmuted, but I wonder if your microphone is turned off perhaps? Yeah, we're still not hearing you. Andy and Kim, I don't know if you guys want to try calling in? Rachel made it work with the calling. Just enter in the participant code.

We've had good luck having conversations via Zoom before with Utah, so this could be just a malfunction on this particular computer. Fadi is still there it says. Fadi, would you ... I don't see you.

Andy: Hello.

Kim: Hi, can you hear us?

Marci Sontag: Now we can hear you, yay, good.

Kim: That's awesome. Okay, we called in.

Marci Sontag: Introduce yourselves first, and then go ahead with your discussion of what's happening in Utah.

Kim: Okay. Did you send her the slides?

Andy: No, I didn't.

Kim: Oh, okay. We have slides, are you able to share your screen?

Marci Sontag: I don't have, do I have your slides? I don't think I have your slides.

Kim: No, Andy said he didn't send them to you.

Marci Sontag: That's fine, you guys are welcome that you can share your screen locally.

Kim: Okay, share my screen. This one?

Andy: No. This one.

Kim: Where?

Andy: Okay. (silence) Can you see our PowerPoint?

Marci Sontag: Right now we're seeing it looks like maybe an email. There's a PowerPoint, yep, we got it.

Kim: Okay. There we go.

Andy: Basically we tried to follow I guess your direction with the questions, right? That starts here, right, no surprises. First screen, 24 to 48 hours. The mean and when it occurs is at 1.56 days. Second screen mandate 7 to 28 days, the actual mean is around the 12th day. We are working on a rule change to get that down to the mandate, we target 7 to 16 days.

Kim: 16 days, yeah.

Andy: That is in the works because of all of the pushback from the community pediatricians, but it should happen within the next half year. Algorithm changes, again, we until it, we are in the last days of use. We have a floating 97% daily cutoff calculation. We rigorously analyzed the last several years of data, and we did, so based on this long term population assessment, we are switching to high cutoff. For the prescreen it will be at 51, which is to standard deviation boundary of the population mean, and then the second screening we change that to 42 nanograms per milliliter. The second, the IRT measurement of the second screen is only performed when the first one is abnormal, and this value of 42 is based on the standard deviation cutoff again of the population mean.

The answer B to your question, we perform the DNA panel in house. We currently use the Luminex X pack 60. We also have validated the Illumina 139 platform, and we are going to explore some form of an external instrumentation, that's some time next year. The variable cost component for the assay I estimate at a little under $15, and that is basically an extrapolation of we have a fee per [inaudible 00:34:44], and then we bring that down to a fee per temple, calculating for controls and standard and so forth. Then we also consider that in most cases, right? We perform the actual test six times-

Kim: For the IRT.

Andy: That's for the IRT part. That's a total of around $15 noninclusive of personnel. The mutation analysis cost we did in a fairly similar fashion, because of the IRT, IRT algorithms we have a fairly long number of DNA tests we perform. On a typical run, we calculated we have about three samples, and then we have two negative controls, and two or three CDC controls. That's why this cost of the mutation count is at $150.

First, data automatically tested are cases where the provider has a suspicion of illness. That's the only exception. We have no ultra high cutoff, because again we use data driven approaches, and the high elevate values, they are due to the fact that there are externalities that are non-genetic cause that affect these values. The whatever was G, I forgot what question G was, sorry.

Kim: Oh, we don't have it in front of us. G is a yes, but I think [inaudible 00:36:27]. Oh, do you have a protocol to test DNA on the first if the second's not available or matched? Yes, we do.

Andy: Okay.

Kim: Yeah.

Andy: Then what's unique about our workflow and program features, so if we identify two mutations, that means an immediate sweat chloride test and clinic appointment, and the newborn is seen within 24 to 48 hours. Seeming that's kind of nonspecific, but that means really treated. If we identify one mutation, that also means we perform a sweat chloride test, and if indicated we make a clinic appointment, but of course it's conditional on the outcome.

The other really unique thing for us and that works extremely well is that our program arranges and pays for the sweat chloride testing, that really removes the major bottleneck of delays. We do genetic counseling, and we of course arrange the CF clinic appointment and follow through with that. That's really the human involvement here, this is the big bang for the buck. The accounting is provided during the sweat test, and again, the newborn screening program covers all diagnostic expense.

When you look at outcomes, so the age of the call out of abnormal results is at 23 days. The age of diagnosis, so with a sweat test that's at a little under 24 days, and the age of intervention is at, that was as of yesterday, at 25.7 days. When you asked us why is there a difference between 23.96 and 25.7, it's simply a question of sample size. When we have the number of 23.96, that includes here we measure all cases that are referred to for sweat chloride testing.

Kim: Or carriers.

Andy: Or carriers will be, we do it here. Yeah, and I think that's all there is, so I hope you have lots of questions now.

Marci Sontag: I just want to comment, and hopefully all of you were able to see the presentation that the Utah group did last winter. If you didn't it's on the New Steps website, that went into some more of those details of how all of those things work, this is kind of a high level summary. I think that's really remarkable, that last slide that you showed, that the time to call out to the time of diagnosis and intervention is a really short window. I think that can be attributed to the good relationship your follow up folks have with your clinical staff, that you're scheduling that sweat test, you're getting them right in, and you're making sure that that baby gets into the clinic. They're reserved, I think, if I remember correctly, there are reserved spots within the sweat test lab for that to happen, and you do it very efficiently.

Andy: Yeah. Marci, you hit, this is really the take home message. This year in the US World and News Health report, our CF Center is one of the top centers now in the country in terms of allowing function. We were when Fadi present we were invited to the presentation of this result by the CF Center, and he really showed the remarkable improvement in terms of, and part of this success story is the accelerated time to diagnosis through the newborn screening program. I think that is really remarkable.

The other thing I want to, I joined late, we should really go back and for the states who have it, and really take a close look, and they can do that in a completely data driven format or fashion. Let's look at these high IRT boundaries. We identify in the first screen, how many of them are really real? I would actually bet that the majority of them are not. They are really due to ...

Kim: If you're talking about the ones that are like 400-

Andy: Exactly.

Kim: Yeah.

Andy: The people who have the data and easy access to query, we should really look at it as a community and ask the question whether that makes sense.

Marci Sontag: That's looking at, across all babies, not just babies with CF. Across all babies of those really high IRT values of what's going on there. Is that ...?

Andy: Yes.

Marci Sontag: Okay.

Andy: Then maybe apply simple statistical tools, like a multi regression or something analysis or variants that you can really ask. That maybe mutation status is not all that predictive, but we have the data, so let's just look at it.

Marci Sontag: Yeah. Yeah, I think that makes sense. Fadi just texted, and this is supporting what you were saying about the could clinic relationship. Their wait for length in 2017 is significantly improved in the first six months of life when compared to 2016. Looking at that earlier time to diagnosis following newborn screening, things are getting better. Presumably from you all working hard to push that time of diagnosis and intervention earlier than it had been previously. That's great, thank you for sharing that, Fadi.

One question that Lani's asking, and for some reason, let me see if I can unmute you on my end, Lani. Not sure why you were ... Lani, are you able to talk now? Might be an issue, because you're unmuted on my end, so it might be an issue with your microphone. Make sure your microphone is on, on your end. I'm going to speak for Lani.

She's asking, for all states, how many times per week do you do IRT testing and DNA testing? I think what I've heard everyone say of IRT testing is happening every day that the lab is open. DNA testing I heard from Colorado was once per week. I don't know if we have that answer from Texas. How often are you doing DNA, Rachel?

Dr. Rachel Lee: We do it daily, Monday through Saturday.

Marci Sontag: You do DNA daily?

Dr. Rachel Lee: Yes.

Marci Sontag: Yeah.

Dr. Rachel Lee: Average sample volume about 20, around 20 a day.

Marci Sontag: Yeah. Yeah, I think many of the states with a smaller number of births are not able to do that, because it's just not cost effective.

Dr. Rachel Lee: Yeah. I can see that why in Colorado and Utah, their costs a little bit higher because of how the number of controls they have to run with each time. That will drive the cost higher.

Marci Sontag: Yeah. Yeah, that makes sense. Stacey, did you have anything else to add to the timing? Stacey or Mark. No?

Dr. Martiniano: We had talked about just in terms of improving timeliness to try to get more, but I think we're limited a little bit by number of samples and cost. It's still something up for discussion I think, but not right now for us.

Marci Sontag: Yeah, I think at one point we had moved in our state to doing it twice per week, and then I think we had to go back to once per week.

Dr. Martiniano: Yeah.

Mark Dymerski: Yeah, the number of samples we're typically analyzing is four or five a week.

Marci Sontag: Okay.

Mark Dymerski: Part of the reason we added that 140 is just show those sooner, and add some of those. Also, we cut back the number of weeks we were waiting for those seconds, so we're looking at those firsts sooner to add as to waiting 30 days or waiting, we moved that up a week. We ended up moving that up a week. Currently we're having that query right at three weeks, 21 days is how they try to keep to that.

Marci Sontag: Okay. Well, that makes sense.

Mark Dymerski: So they're not sitting out there that long, the seconds, or we're not getting the second in, in a timely manner, that's sitting out there 28 days, it's 21 days. We're trying to move all that to push them that way, so we can work the timeliness that way.

Marci Sontag: Okay. Thank you. Utah, how often are you running DNA? I think you guys are muted.

Andy: Can you hear me?

Marci Sontag: Yep, can hear you.

Andy: Okay, so we are running it once a week. We have a flexible approach, because we kind of based on statistical prediction we can kind of predict. We're a little bit flexible, if we have two or three cases on a Monday or Tuesday we run it sooner, right? Otherwise you wait until the end of the week, but I want to echo what Colorado said. The biggest bang for the buck is enforcing that the second specimen is collected more timely.

Marci Sontag: Yeah.

Andy: Because that's where we have really the biggest benefits, and that's why we are pursuing the rule change.

Marci Sontag: Yeah. It was notable that your rules now say up to 28 days. That's a long time, so I'm glad that you are pursuing that rule change. Everyone may have seen the note from Iowa, that Iowa is running IRT and CFTR a few times a week. We've reviewed the cost and it's just not financially feasible to do it more often. Also that Oregon has lost power in the lab, so Oregon might not be presenting, although I think Sasha Cornell is on, and she's the clinician who's working on the CF side. Sasha, are you able to talk?

Sasha Cornell: Yes, can you hear me?

Marci Sontag: We can hear you.

Sasha Cornell: I'm actually, let me see if I can get my screen to share.

Marci Sontag: Okay.

Sasha Cornell: There we go. How's that?

Marci Sontag: Got it.

Sasha Cornell: Okay. I just, the lab was going to fill in for some of these questions, and I'm not sure what to ...

Marci Sontag: [crosstalk 00:47:25]

Sasha Cornell: What's that?

Marci Sontag: Just do what you can.

Sasha Cornell: Okay. Let me just see. Okay, so I just took your email and answered the questions. We just started this algorithm, we are using, initially we had just been doing IRT, IRT, and we had cutoffs of 90 and 60 I should say, in that order. We have now changed both to 60, and we only run IRTs, and this has historically been true, on the second specimen if the first was elevated. If the first was normal, they do not get a second IRT.

The DNA panel we use is a-

Marci Sontag: [crosstalk 00:48:16]

Sasha Cornell: Yeah?

Marci Sontag: I'm still seeing your first intro slide. I don't know if you've moved on to your second slide or no? Maybe. Go ahead. I didn't mean to interrupt, I just thought maybe you had words on your slide that matched what you were saying.

Sasha Cornell: Can you see, it says IRT, IRT-DNA algorithm at the top?

Marci Sontag: No, I'm seeing the CRF timeliness webinar title slide.

Sasha Cornell: Okay, hold on a second.

Marci Sontag: There we go.

Sasha Cornell: Okay. There we go, sorry. I think it only shows one desktop.

Marci Sontag: Yeah.

Sasha Cornell: The DNA panel that we use is a 23 mutation panel, and I can't remember which company it is, but it is commercial. The cost of running the IRTs and DNAs I'm gonna refer to my lab folks on that. As I mentioned, we only run IRTs on the second specimen if the first is elevated. We don't have any automatic referral to DNA, and we do have an ultra high cutoff of 140 that will result in a recommendation for sweat testing even if no mutations are identified. Then we also, if we don't receive a second or if it's unmatched or if the first was unset for some reason, we will then run IRT on the second specimen, and potentially go back to the first if we don't get a second by 30 days of age and run DNA on that. We haven't had to do that yet, so we'll see how that goes.

Then we do sort of unique to our program, and this comes out of a time when we were just doing IRT-IRT, we had set up an early notification algorithm that if the first IRT was over 140, the lab would notify me and we would both call the PCP, and strongly encourage them to send the second specimen in a timely manner. Also, in the state of Oregon, they would have the option of using a courier service courtesy of New Steps. Again, if the IRTs are over 140, and we don't find mutations, we still refer for sweat testing.

Then lastly, just we haven't been doing this for very long, we've had five call outs so far. One was a CRMS, one was an early notification with a first IRT upwards of 200, and then the second IRT was normal, and so that closed that case. Then we've identified three cases of cystic fibrosis. Our time between, I don't think it's changed our timeliness in any substantial way to add DNA, although it does add a little bit of time on the back end. It's still about five to six days between when we get notified and the patient being seen in clinic.

We are a big state, and it takes a while for people to get here, and we're also limited by the fact that there are now only three places in the state to get a sweat test; Bend, Medford, and Portland. We are struggling with that sort of critical access problem, and we're actively looking into trying to get Salem to

start doing sweat testing again. They had previously done it but were asked to not do it because they weren't following recommended testing procedures, so we're going to re-approach them and see if they'd be willing to do it now.

That's all I had, and I can answer any questions that I can answer, and then we might need some lab folks for some other ones.

Marci Sontag: I don't see the lab folks on the call yet, I'm looking for them and I'm still not seeing them, so the power must still be out. Did you answer the question of how often they're running DNA?

Sasha Cornell: I want to say they're doing it twice a week. That was what we had sort of agreed on.

Marci Sontag: Okay.

Andy: How old are the children when they are diagnosed?

Sasha Cornell: They are by and large still under 30 days of age, but it's usually they're in the 20 day, upwards of 21 days. Between 21 and 28 days.

Marci Sontag: Yeah, there's only a few cases, so it's hard to say that with too much confidence at this point.

Sasha Cornell: Well, we've also had one really frustrating outlier where we called the PCP and asked them to get the sweat test quickly, because there was one mutation found on the lab panel, and it took them two weeks to get the sweat test, and then it was positive. The pediatrician didn't notify me until the following week, and so that kid is going to be almost two months of age by the time they actually get in. There's nothing you can do about stuff like that, it's just education of that primary care doc, and I don't know. It's been a really frustrating case.

Marci Sontag: Yeah, and I know that's a big chunk of what you guys are trying to do with the New Step 360 project is try to help get those second specimens in, and decrease that time to diagnosis for CF.

Sasha Cornell: Yeah, and even with that one, we got the second screen in a timely manner, it was just that it was completely dropping the ball after that. It wasn't us, it was the pediatrician, and then the family lives in the middle of nowhere, literally, and could not actually come to Portland for a visit. We tried to get them in last week and they refused, so it's like, what are you gonna do?

Marci Sontag: Right. Right, and there's always those outliers, there's always those challenges of trying to fix the individual cases in the system.

Sasha Cornell: Right. I think we have set up enough fail safes to minimize the cases that we miss, and with barring disasters like this particular case, getting kids in as quickly as we can. I think we're achieving that.

Marci Sontag: Good, good. Is this now in place for all of the other states that Oregon is screening for, or is this just Oregon specific now and those other states will be added later?

Sasha Cornell: No, they are screening DNA for everybody now.

Marci Sontag: Okay. Those are not large states, but you will have more data on what's going on in those states that the Oregon level, you don't have that specific-

Sasha Cornell: Yeah, I don't have call outs for those other states, but I'm sure Sarah would.

Marci Sontag: Okay. Stacey asks, can you ask that the lab call out positive sweat tests to the CF center?

Sasha Cornell: Well, so, this particular lab, they mailed the results to the PCP, which is part of the problem. My understanding is that a positive sweat is a critical lab value, so any time we get a positive sweat at OHSU, I get paged by the lab. I felt like this was an unusual circumstance, and I actually, I had already been planning to do this, but it makes it even more important. We're going to actually go to that sweat lab, and review their procedures, and talk to them now about notification, because they're not notifying people appropriately it seems like.

Marci Sontag: Okay, yeah. Rachel Lee, everyone's typing questions rather than just asking them, and they're making me ask the questions. Rachel, I'll be happy to ask your question, because I know you're so shy. Rachel wants to know what are the false negative rates for each state? I think for Colorado we've answered that, we haven't calculated recently, but I think it's less than 5%. Stacey, does that sound right? Stacey and Mark.

Dr. Martiniano: Yeah, we've been seeing two to three. We've only had a couple lately, so I don't know.

Marci Sontag: Yeah. Rachel, what is it for Texas?

Dr. Rachel Lee: For Texas it's about 3%.

Marci Sontag: Utah?

Kim: Yeah. The percent, I don't know. I can think of one missed case a couple of years ago, and then the family, it turned out to be a pancreatic sufficient mutation. I think we've only had like one case in the last couple years, so it's low.

Marci Sontag: Yeah.

Andy: It's again that it really falls down to the definition, right? Strictly speaking, if we look at high value, are we missing based on high value IRT? No, we don't. It's the other, these unusual cases that are the non-classic CF or pancreatic sufficient, structural abnormalities, these kind of things.

Marci Sontag: Yeah, and Andy, that is a challenge. I think most of what screening programs are aiming to get the pancreatic sufficient kids as well. We're redefining CF now, it's CRMS and where is that lower boundary of who we're trying to find? I think it is an important issue of who we're aiming to get with each of our newborn screening programs.

I'm going to say that Oregon is too early to be able to answer that question, since they've only been screening for a couple of months.

Sasha Cornell: Correct.

Marci Sontag: Any other questions? I'd like to say, I'm sad that the Washington group hasn't been able to be vocal, so I've been trying to ask their questions for them. It was because of them that really we had this particular webinar. They are trying to do as much data gathering as they can as they are trying to decide what they are going to do moving forward. They're currently an IRT-IRT state, and are looking to see how they can improve their sensitivity and withouts and their specificity for their newborn screening program. They have been asking questions via chat, and they might be reaching out to some of you directly. They reached out to Colorado to ask us some questions about our program.

Carol saying Iowa quotes 2% to 3% false negative as well. Iowa uses an IRT-DNA algorithm. Is anybody else from other states, I see we have quite a few other states who aren't two screen states, and I've only been picking on the two screen states. Are there others who would like to comment on that or anything else?

Andy: Well, I think on a national level, again, I want to really urge because especially for the IRT-DNA space, how do you account for the additional costs? Considering that 80% to 90% of all elevated IRT values, they have nothing to do with CF, how do people account for that in their fee structures? I think that this is a really big problem, and this contributes to the overall newborn screening cost, and we need to get a handle on that, right?

Marci Sontag: Yeah, Andy, I think that's a great point. Who's actually paying for those costs that are, especially with genetic counseling, the calling those kids back in, the increased number of kids that are being identified related to IRT DNA or whatever other algorithm we're using that the kids are being called back. I think that's the advantage that these two screen states have is decreasing the number of children or families who are being impacted by false positive newborn screens.

Dr. Rachel Lee: Just one comment, this is Rachel, and it is true that using IRT-IRT, when we do second screen IRT, we do see that, but 80% of first screen with elevated IRT become normal. Off the remaining 20% that that reflects to a CF DNA panel, it's about only 10% of them using our new panel that has the mutations, and about 90% of them are with zero mutations. That's what we've found so far, that we were able to reduce false positive rates, the number of presumptive positive report out using this algorithm.

Marci Sontag: Yeah, that's great, Rachel. I think that's kind of the key fact is that second IRT is able to make it more specific, and you're able to sort out those kids that their IRTs are elevated for some other spurious reason that's not related to CF.

Andy: These numbers are the same for all programs. Rachel's numbers are exactly the same as ours.

Kim: Yep.

Marci Sontag: Yeah, same here. Rachel speaks for all of us.

Dr. Rachel Lee: We just have a little bit more births, that's all. Just a couple more.

Marci Sontag: Yeah. All right, well, I'd like to thank you all for your participation, and we will be posting the webinar on the New Steps webpage, so if you have others, I know there were some people who weren't able to be on today, so if we others who would like to listen to this conversation. Really, I'd like to thank you all, because this really was a conversation, and it was great to be able to ask questions and have everybody be able to learn from each other.

Lani Culley from Washington, we missed hearing your voice, but I hope you got some of your questions answered. I think this was helpful for all of us, so thank you all, and we'll be looking forward to talking to you again next time.