Marci Sontag: Hello everyone, this is Marci [Sontag 00:02:23] and I'm going to give everyone just another minute or so, and then we will get started.

All right, well hello everyone and welcome. This is Marci Sontag from New Steps 360 and the Colorado School of Public Health. We are very excited to have you all here for our five month cystic fibrosis newborn screening timeliness webinar. And we're looking forward to really having an interactive discussion about some of the new data that has come out on the Cystic Fibrosis Foundation that has been updated very recently.

And so, with that I would like to say that I am very excited to introduce Dr. Susanna McColley. Susanna McColley is a professor of pediatrics at Northwestern University Feinberg School of Medicine and she's also the Vice-Chair of the CF Foundations new branch in quality and complaint consortium.

However, Dr. McColley has been held up in a clinical commitment and will not be able to join us today. So, I will be presenting Dr. McColley's slides on her behalf.

So, I have been very familiar with the data the CF foundation has been collecting and I will do my best to represent her. She's hoping that she will be able to be on the call shortly and be able to help us with some of the data questions as they arise.

So, with that I will continue, doing my best Susanna McColley impressions. So, today what we had asked Dr. McColley to present were to first review the efforts to evaluate the newborn screening programs specifically related to newborn screening using the CF ... Or within each state using the CF Foundation registry data, and to review the age of diagnosis. This is already ... Many of you have seen this data previously. Previously, data that was collected between 2010 and 2012, and we've been asking the CF Foundation for updated data for the past couple of months and we're very excited to be able to present that today.

So, this is specifically related to the age of diagnosis, the late diagnosis, and the false negative tests in nine periods, and looking at it at each state level. So this is data that is entered by the CF Centers and according to the CF Foundation. And then in reference to much feedback that we have given to the CF Foundation and that we have since received from all of you in the newborn screening community, we're making some changes on how we collect and report this data. And we're going to be talking about the planned changes in the registry to more accurately capture some of the data produced [inaudible 00:07:24] up to diagnosis and initial treatment, and the diagnostic confirmation.

And if you are familiar with this data, the reasons for those proposed changes should become apparent as we move through.

So, the CF Foundation newborn screening quality improvement consortium was formed many years ago really as the newborn screening was being implemented widespread over the United States. And this was to really help programs as they were implementing newborn screening and develop quality improvement programs to work towards earlier diagnosis, better sweat testing, and better care of the infants that were diagnosed by newborn screening.

This QIC was really developed under the leadership of Dr. Gill [Parrel 00:08:23]. He has representatives of CF centers in all of the states and Washington DC to be liaisons to this program, and there was really, initially, one member per state to represent what was going on in their new state newborn screening program.

So, much focus of the initial program was on the newborn screening process and the follow up program, and timed diagnosis, and in addition to that, how we cared for those infants in the first weeks and months following a resulting positive diagnosis from newborn screening. But we know that the age of diagnosis and the number of false negatives are really key quality measure that were identified by the CF Foundation to measure the success of newborn screening programs and the CF center programs that were following these infants.

So, the CF Foundation reach of registry really is been touted as one of the examples of patient registries throughout the country, and has been utilized to asses age of diagnosis, and then to compare program results across different state newborn screening programs, across CF centers, and that really then fosters learning and best practices. And the CF Foundation has done a fantastic job in helping us to understand the best practices and to lead the way in quality improvement between newborn screening programs and really between CF centers.

So, the CFF Patient registry is a [post-pective 00:10:12] observational database. This has been going on for many decades now and it really has evolved over time to be initially an annual data collection tool to now being a very sophisticated collection tool. It is overseen by a committee that includes physicians who are following these children to really identify what are the best variables to be collected, and we have them typically been collected in what are the questions that are being asked of CF staff.

This registry is provided ... Is governed by informed consent by the patient. So, anybody who is participating in this registry, the registries are overseen by local institutional review boards, or IRVs and the patients or parents provide informed consent. Having said that, the initial concern was that the informed consent would lead to low participation and maybe people would want to opt out, wouldn't want to participate. However, the CF community really has had very high participation and we see really good participation by parents and patients, and there's a large number of patients in the CF Foundation registry, and I think it's estimated to have more than 90% of patients from the US as being represented in the registry.

The CF center staff enter that data into a secure website and they enter data that's very comprehensive. It's basically the diagnosis, which is what we'll be talking about today, but then also the treatment, their outcomes, pulmonary functions, and various outcomes, their growth outcomes, the treatment, what therapies are they on, how often do they take those therapies, and the complications. So this is a very rich data resource that the CF Foundation has developed.

But, we all look into these ... The CF Foundation registry with some level of envy I think because it's able to be incentivized by CF grants that are provided to CF centers, accredited CF centers who enter their data into the registry, and for each complete confirmed diagnosis, and complete data sent, the CF centers are paid as part of the CF center [inaudible 00:12:47]. I mean, that helps to support their overall system within the CF center to include their clinicians and followup folks, their clinical staff and clinical team within that group.

The data from the CF Foundation registry has been the basis of numerous publications over the last many decades and has really provided a lot of very valuable information to the CF community.

I just got a message from Susanna that she's able to call in. I don't see her yet. So, I will continue in her absence and-

Dr. Susanna McC: Marci?

Marci Sontag: Are you there?

Dr. Susanna McC: Can you hear me?

Marci Sontag: Yes.

Dr. Susanna McC: I am here.

Marci Sontag: Excellent.

Dr. Susanna McC: I ... You're doing such a great job that I didn't want to interrupt you, but I also can't see the slides. My zoom length isn't working. I tried it both automatically and manually. So ... And I'm also in a noisy place because my doctor, nurse says, "You know, go do your call and then come back." So, I'm going to let you go through the slides. You're doing a wonderful job. And then I will un-mute again when you're done to take questions. Is that okay?

Marci Sontag: That is fine.

Dr. Susanna McC: Thank you.

Marci Sontag: But please feel free to step in if I misstate something or if you'd like to add something.

Dr. Susanna McC: Okay.

Marci Sontag: So, continuing on then, the diagnosis in the CF Foundation registry is entered as a date of diagnosis as a single date. And that single date, if we look, is based on what the CF Foundation's guidelines are for diagnosis of cystic fibrosis, and if you follow those guidelines strictly it would require, historically, a sweat test and/or a genotype, but having two different data points is a yes, we can confirm this patient truly does have cystic fibrosis. So, a sweat test repeated on two different days or a sweat test and a genotype reflecting CF 2 mutations that are consistent with fibrosis.

However, we know that there is some variability in how that's come into. And many clinicians might see the positive newborn screen and it might come back with two mutations. They see the patient, see the patient clinically, upon assessment, has cystic fibrosis and say, "I can make a productive diagnosis here and I will call this the data diagnosis, where other clinicians are more likely to follow the rules of the consensus conference guidelines and say, "We need to wait till that sweat test has happened. So there's definitely some variability there.

Within that diagnosis in the CF registry, on that page, there are many reasons for the diagnosis than can be listed. And those reasons can include prenatal testing, positive newborn screening test, family history, or symptoms. And really there are even more reasons for what those symptoms are. Is it symptoms from GI problems, or symptoms from respiratory issues? There's a longer list.

And so, many of them can be checked. So you can check more than one of those and say, "Well, there's a family history. But there was also a positive on newborn screen." So that you could potentially present, or select more than one within the CF Foundation registry.

And then the sweat test result is also collected on that diagnostic page and it is highly, or strongly suggested that every patient who has that newborn screen, or has that sweat test, date and results entered, but it's not mandatory in that you can complete that diagnostic page without that. Then we also have the date of sweat test. So, the date of sweat test and the date of diagnosis might not be the same.

So, the initial efforts to asses the date of diagnosis, when you look at the initial data that the CF Foundation put together with the help of Susanna and others several years ago, you would say, "Well, there were some babies who were diagnosed before they were born." Which is remarkable and really could have been done with a high number or prenatal diagnoses, which was happening, especially in the New England region. So the date of diagnosis was going along with the date of prenatal testing, and then may have been a couple of months before the birth of the child. So that was hard to reconcile why some babies were diagnosed before they were born and others weren't.

And so, because of that, that's not really reflecting the date of ... Or the performance of a newborn screening system, but more the performance of the overall healthcare system within that state. We had to kind of reevaluate how we were collecting that data and evaluating that data. So, we were going back to the CF Foundation and saying, "We would like to utilize dates of diagnoses that happened anytime after the birthdate." So, it could have happened the day of the birth, or the day after, because that makes more sense and kind of normalizes everybody. So, at least you can't ... Aren't diagnosed until the baby actually enters the world, and then evaluate utilizing the dates, day of life seven or later with the kind of understanding that's really more likely when those diagnoses would be happening following newborn screen.

As part of this process, we define that late diagnosis after a positive newborn screen is greater than 60 days. So, thinking that end diagnosis following newborn screen, we should be able to go through all those processes and get a diagnosis within 60 days of life and set that two month period, saying, "That's kind of late for a newborn screening diagnosis to be made."

And then, define false negatives as those in that greater than 60 days and less than 365 days that didn't have a positive newborn screen reported, who were born in a state who was performing newborn screen. By the state of this data that I'm presenting here today, all 50 states were doing universal newborn screening for cystic fibrosis.

So, this eliminates the most complicated meconium ileus because we know that there are reports of infants with meconium ileus being more likely to have a false negative newborn screen. Or IRTs that are below the cutoff in a given state. And then, the upper age is based on that historical average age of diagnosis of pancreatic insufficient patients that would present clinically. But, it could potentially underestimate the results of the test.

And so now, to the data. And these are the data that were reported through the CF Foundation page and registry between 2013 and 2016. And this is purely the number of newborn diagnoses in each of those states. And you'll see the blue line is total CF, the red line is total CF that are diagnosed from newborn screening, and then total with any diagnosis. And you can see this really more reflects the size of the state, and the population of that state, as California is on ... California, Texas, Ohio, New York are bigger states, are on the left side of this. And then going down to our smaller states on the right side.

And so, that's just so to clear up any confusion, the CF Foundation collects data on CRMS, which is cystic fibrosis related metabolic syndrome, or CFTR related disorder. And so you'll see that in the state of California, we see many more CFTR ... Many more of those infants or individuals with a total ... With any CF diagnosis. That green line California is proportionally much higher than the other bars in California compared to many of the other states. And that's really due to the algorithms being used in California where they're doing the focus sequencing on patients following a positive newborn screen and one mutation.

So, I'll let you absorb this slide for just a minute. Find your state and see if the data looks similar. And these are data then that are reported by each CF Foundation accredited center and then collated by the CF Foundation and put into data that's representing each state.

And so then we look at the median age of diagnosis by state. And so these are eliminating those who were diagnosed before their date of birth, so these are those that were diagnosed the day of birth, and this is the median age of diagnosis. So the diagnosis made one day or later after that birth. And so you see the median here across all states was just over 15 days. And you can see that it varies here, reportedly it looks like about two days up to about 32 days for each of those states.

Data are presented here by each state with the lighter green bars representing states that have two screens. They're using and IRT IRT, or IRT IRT DNA algorithm. The CF Foundation several years ago set a goal of 15 days of diagnosis as being the median. 50% of all our babies should receive that diagnosis by that point. Now, again as I talked about earlier, this goal here is that ... I'm sorry. I just got a text message that I will respond to first. So, the message that many of you might see, Claudia's pointing out that I mentioned that the goal for diagnosis was 60 days, and the slide says that the goal is 15 days.

And so, really, we'd like to have the median of diagnosis be 15 days. And that 60 days that I mentioned earlier is that that's a late diagnosis. We'd like to have everyone diagnosed, the CF Foundation's goal is to say everyone should be diagnosed by 15 days of age, or the median is 15 days of age, but if it's later than 60 days, we're going to call that a late diagnosis. And that's important for the slide that I'm going to present shortly about late diagnosis.

So, you can see that in general, the states with two screens are a little bit later than those with one screen, which makes sense because it takes longer to get those two screens in. And I know many of the two screen states, including those who are on the phone today are really doing a lot of work to move that date of diagnosis to an earlier time. But, thinking about what date of diagnosis means here, I think we're still struggling because in those states to the farthest left, it's hard to imagine that a true diagnosis including a sweat test is happening at stage before life, and that might be what those states on the far right are doing, is they're making sure that that date of diagnosis only occurs after those ... That [inaudible 00:24:52] diagnosis happens.

What we don't know here is what algorithms they're using to really reflect that. Is this ... Who, as the state newborn screening programs are entering ... Not the state newborn screening ... As the CF centers are entering this data, what criteria are they using to determine that the date of diagnosis is confirmed?

So, I'm looking at some of the other questions in the chat box. [Spotty 00:25:25] says, "We believe the slide looked like certain states timed a completion of newborn screening and not timed the clinical diagnosis."

Which they'd definitely be the case on those who were on the left side. I think that might be true that with the reporting out of newborn screening might happen then. Although I would even suspect that might be early for that as well because it's just the timing of the newborn screening process might not really be happening. Getting those results, and then doing a DNA test and getting results reported out. So it probably also includes some other diagnoses including the meconium ileus or prenatal diagnoses.

The other question in the chat box is does two screen mean two specimen states? Yes, in this case two screens as I refer to it means two specimen states in most cases, or states that use a model that's similar to what two specimen states are doing. The IRT IRT model, even if they don't routinely collect two specimens on all newborns.

So, I'm going to move on from this slide. During the discussion, when we bring Susanna back in, I'm happy to come back to this slide and you con comment on that.

Oops. I went the wrong direction.

And now the median age of diagnosis of all infants with positive newborn screening. So this is now just taking out those infants who had a positive newborn screen. And data represented here, the blue bar for each state is presented as the median age of diagnosis between 2013 and 2016 and then comparing it to what we saw in 2010 to 2012. So, this would allow us to see have there been any differences?

So, again I will let you find your favorite state and see if you see any remarkable changes over time. And you see in many states that gray bar is significantly higher than the blue bar, which means we are moving to having a shorter median age of diagnosis in the later time periods. The quality improvement activities that have been going on in various states have worked towards shortening that time to diagnosis following a positive newborn screening. That's not true for all states. I will caution you, in smaller states differences in those bars might look like one or two infants with a slightly longer time of diagnosis. So, it might not be reflective of true changes in the data or it might be more reflective of just small data.

Moving onto the next slide. So now this was ... Previously, we were just limiting the data to those who were diagnosed after birth. This is now those who were diagnosed at greater or equal to seven days after birth. And that's to get away from those diagnoses that are really not very likely to be due to newborn screening. Thinking that diagnosis day three of life, as I mentioned earlier, is really not likely to happen following a positive newborn screen because chances are very good that newborn screening specimen has just reached the lab by day three of life. So, it's not likely that the results are back and reported to the family, and the diagnosis made.

So, when we eliminate that, we can say, "Well, now when are babies being diagnosed?" You see, we now have that median age of diagnosis more at the day of life ten or greater. And you can see, again this has happened to ... You can see the changes between 2010 and 2012, the orange bar, and 2013 to 2016 in the blue bar. And again, I'd like to point out that for almost every state, that orange bar is much higher than that blue bar. May reflect small numbers, but I think the trend would show that we are doing a better job of diagnosing infants earlier following positive newborn screen in the later years of this report.

And now let's go to the late diagnoses. And these are, again, as we talked about earlier, this late diagnosis of being greater than 60 days after birth. And you can see this is the percentage of late diagnoses. So, of all the diagnoses a state had, in those time periods, what was the percent of them that were being diagnosed greater than 60 days after birth? And you see on the left side here we have this divided up by 2013 to 16 on the top, and then 2010 to 2012 on the bottom. So, we'd like to see are we doing better. CF Foundation again has said less than 10% of the babies should be diagnosed after 60 days after birth.

And so, you can see that there are many states who have zero or very few, a very low percent of babies who are diagnosed 60 days after birth, and then some other states who have 20, 30, in some cases up to 40% that are diagnosed greater than 60 days after birth. Now, again, we need to interpret these data with caution as we may very likely be seeing this due to differences in how we are all ... Each newborn screening ... No, each CF center is defining diagnosis. So, we don't know ... Two things we don't know. We don't know what they are compared state to state. And we don't actually know if a state has changed their ... Or not a state, a CF center has changed how they report these data in these time periods.

So, they may have said, "You know what? In the 2010 to 2012 era they reported it as the time they made a presumptive diagnosis. And then maybe in the 2013 to 2016 era they saw some of these data and said, 'No, we actually need to say it's after a sweat test.'" So it's hard to even compare within a given state or CF center how that compares from period to period.

And now we have the diagnoses after a false negative newborn screen. So, how many babies have these ... What's the percent of babies that have been missed by newborn screening in a given state? And so you can see many states are reporting, or many CF programs are reporting that they did not identify any babies as a false negative through newborn screen and then probably more typically we see in the five to ten percent range, and that's what's been reported in the literature as well, that our IRT algorithm really doesn't do ... Or IRT assay doesn't do that great of a job identifying every baby with CF through newborn screening, so this is pretty typical. We're going to see three and a half to seven and a half percent maybe is pretty typical for what we're going to report in CF newborn screening as false negatives.

Some of these states on this far side were using an IRT IRT model that had a relatively high cut off and have recently changed to an IRT IRT algorithm and have lowered their cutoff significantly, and we anticipate that these false negative rates will drop pretty soon.

And there's a ... I'm going to go back to this slide really quickly, as Sasha Cornell has pointed out, this data would be more useful if it was presented as actual numbers of false negatives. And it's true, because some of these states that are also on the right side here, meaning Hawaii, Idaho, and Alaska are very small states that missing one baby can really have an impact on that false negative. So, having these data in raw numbers would also be a very useful approach.

So, now just looking at the age of first sweat test and first clinic visit, and doing some comparisons of when does it look like this is happening and when are patients getting into clinics. You can see the baby here, the sweat test tends to be happening earlier than the first clinic visit. And this is accurate data over the entire country. But you see in 2010 to 2012 we see a median of 34 days with a pretty broad range of when that sweat test is happening. And the clinic visit was at 48 days, so that's two weeks later than the sweat test. That gap is shortened a little bit in 2013 to 2016. We see the median of the sweat test happening in 30 days, and then the median of the clinic being 41 days. That means that sweat test is happening eleven days after that sweat test. So, that's something I know the CF Foundation is really focusing on.

And so, we're getting to the end and there's some more questions in the chat box, and I'm having trouble multi-tasking and reading the questions and doing the presentation. So, I'm going to finish the presentation and then we can open up for questions, and I also have Alexander [Elbert 00:35:00] as well as Susanna McColley on to help answer the questions.

So, based on these estimates, using these various definitions we know that the timeliness of the CF newborn screening has improved. We're doing better. We're getting patients presumably in and that diagnosis is happening earlier. And that is also a reflection of all of the work that is going on in CF newborn screening programs to improve the entire newborn screening system and timeliness for all disorders.

So, kudos to the newborn screening experts who are on the phone who've been really working hard to move that far and get those numbers to be ... The diagnoses to be happening earlier. So, at CF centers, the median age of diagnosis has decreased by about seven days from that earlier time period of 2010 to 2012 to the current time period now.

So, while almost all states have medians that are less than 30 days, we're still having many who are diagnosed late, many babies who are diagnosed late, that are diagnosed after 60 days of life. So, half have greater than ten percent, and that's something we really need to work on is those late diagnoses. However, as I said earlier, what is that meaning of diagnoses and as we're waiting for the sweat test even though that infant might very likely be being followed. And so there's some different ways to be looking at this data.

And false negatives may still be an issue. 17 states have greater than five percent false negatives and six with greater than ten percent. Now, as I said, there are some states that are definitely working on those numbers and improving their algorithms. So, as Susanna points out here, this could also represent the way diagnosis after a true positive screening test, but the data wasn't entered as a true positive screening test, so there might be some holes in the data that we need to look at and make sure those really are false negatives.

So, there needs to be some changes in how the CF Foundation patient registry collects data to more accurately define that age of diagnosis. I've mentioned several times that this is a challenge. And that's both can be used for quality improvement and quality control purposes. And it helps us to compare data between states if we're entering it and collecting it in similar ways.

So, field changes that have been proposed, and I will let Alex talk about why these are important, is that presumptive diagnosis is the day that which infants presumed to have cystic fibrosis. So, we haven't confirmed that diagnosis yet, but we're going to treat that baby as if the baby has CF. And this may come because they have two disease causing mutations on our CF newborn screening test. They have that positive newborn screening test and they're also showing symptoms that are consistent with CF, or there's known carrier parents and an eco-genic bowel on prenatal ultrasound.

So, all of those things may lead to a presumptive diagnosis, and the clinician may then say, "You know what? I'm going to treat this patient as if he has cystic fibrosis while awaiting the positive sweat test or a confirmatory DNA test from the sample that was drawn directly from the infant."

Another field change is to get the date and treatment was initiated. When was the change ... When was care changed on behalf of that infant? And that's the prescription, the medication, or other treatments. So, it might be a salt supplement, it might be pancreatic enzymes. So, when did that happen? And that's really, I think, the goal. When did somebody make a decision to change the care of that infant?

And then, finally, the day treatment was ... I think it should actually be date diagnosis was confirmed, not treatment was confirmed. The date the diagnosis was confirmed on that infant. So, we know for sure that there was a sweat test or the results came back from, as I said earlier, a sample that was drawn from the baby and the CF mutation analysis was confirmed in that way.

And then, we do need to have specific question as to whether a false negative newborn screening test had occurred. That right now the CF Foundation is kind of making some assumptions based on how the data entry happened that if you didn't check, yes this was following a positive newborn screen, and the baby was diagnosed at 6 months of age, they're assuming or kind of concluding that that was a false negative diagnosis where in fact it may just be differences on how data was being entered.

So, with that I think I have reached the end of the slides I have. So, I'll leave these up and I'll open it up for question and discussion. And first I'd like to say to Alex and Susanna, if you would like to step in and correct anything that I misstated, please do so. Or if you have any clarifying comments or thoughts.

Dr. Susanna McC: Hi Marci, it's Susanna. And I think you did a fabulous job. I just have a couple of additional comments that are over a number of slides. But I'll start with one related to some of the field changes that Alex and I just discussed by email yesterday, which is that it maybe good to have a definition that is timed to event, that's either a sweat test or initiation of treatment. As we've discussed, sometimes in states that have large rural populations and bad weather, at least seasonally, and I'm thinking specifically of Colorado, people may well be treated before having a sweat test and under ideal circumstances there's a sweat test then it's positive treated the same day.

We've also all discussed that treatment may proceed what's entered as a clinic visit. So, the time to event it's a summary of a number of different things, but it could get a better snapshot of how babies are getting in for diagnosis and treatment.

A couple of other things, one of the things that [Farrel 00:41:33] liked to just point out pretty much every time we talk about the late diagnosis is that in the CF registry we will always miss any fatal diagnostic delay, and so this would most likely have to do with an abdominal catastrophe or hyponatremic dehydration. But it's a caveat to keep in mind.

I appreciate the concern about using the raw numbers for false negatives as opposed to the percent, and that's certainly data that we have.

And then, lastly, I was thinking about this a little bit as you were speaking. One of the things that we may want to think about is how we can asses any kind of pre-diagnosis more vividly. And I think that's something that we could leverage using the registry data as well, and the question is whether any additional therapies should be displayed.

So, Alex, I'm glad that you were able to make it. Do you have additional comments on this or anything else?

Alexander: Thank you Susanna, thank you Marci.

Yes, I can say from the perspective of the registry, right? That registry itself sometimes is capturing the data that maybe biased users who enter the data ... I don't know if I have the ability to share my screen, but I can show you how diagnosis page look. I am pretty much sure than many of you know. How does it look.

Marci Sontag: Yeah, so Alex, you can definitely share your screen. I stopped sharing mine, so if you just go down to the bottom, there's a share screen button.

Alexander: Uh-huh (affirmative), okay. Let me try to see. Can you see my screen right now?

Marci Sontag: Yeah.

Alexander: Okay, you see the screen with patient diagnosis?

Marci Sontag: Yup.

Alexander: Okay, so as I'm scrolling through this, as you can see they are capturing the date of diagnosis. I saw some comments and questions that were asking. So, what do we show here? Actually, showing date of diagnosis. This field that I'm highlighting right now, and we are comparing age at diagnosis as it was entered by users. So, sometimes we also have questions because this age of diagnosis, we don't know. We don't have strict guidelines what is date of diagnosis that we can forward to our users. Sometimes, even I heard questions do we need to say the state of diagnosis at the time when we said something to parents that he maybe has CF? Or is this a case for positive DNA result? Or sweat test? So there is some confusion about data entry into this field that may affect results as well.

Then, as you can see, another comment how we capture newborn screening for the patient. As you can see, it's entry number 15. So, I think there is a question, but I cannot hear it.

Marci Sontag: I don't think so. I think that was just some feedback. I think you can go ahead.

Alexander: Okay. So, the newborn screening is captured as entry number 15. So, I'm pretty much sure that users who are going through the screen trying to see that diagnosis was suggested by something, right? They're finding let's say DNA analysis first, clicking it, right? And they don't go further through the list of other symptoms to select this newborn screening and selecting it. So, what we see in the data that some of the patients have some first CF event, I am trying to use this terminology, to define as the date of the first clinic visit, or the date of DNA, or the date of a sweat test. So, they really have their first CF event within the 30 days after birth. However, they don't have this option newborn DNA test screening check.

And this kind of highlights importance of changes that we need to bring to the patient diagnosis page.

Marci Sontag: Okay, I'm going to ... I don't know. I'm getting some feedback from someone.

Alexander: Yeah, there is background noise, and I'm not sure.

Marci Sontag: I'm going to ... I'm muting everyone on ... Oh, now it sounds like the background noise has ended. I'm going to hope it's good. It's easier if we can just keep all the lines open. So, mute yourself on your own phone if you can so we don't have the background noise.

I'm going to mute everyone. Sara, can you remind me what's the code for them to unmute themselves on their phone?

Sara: \*6 to unmute yourself on the phone.

Marci Sontag: Okay, \*6 to unmute yourself on your phone, and if you're on your computer you can unmute yourself at the bottom left corner, there's a little mute button. So I'm muting everyone now.

All right, so that helps a little bit with that background noise. So, if you have trouble un-muting yourself, please put it in the chat box.

Carol Johnson: So, this is Carol Johnson. Can you guys hear me?

Marci Sontag: Yeah, we can hear you Carol.

Carol Johnson: Okay. So, I'm going to ask a really elementary question, and I apologize if it's one of those stupid moments of mine, but when you are reporting data for a state, is that data a combination of all CF centers in that state?

Alexander: Yes.

Carol Johnson: Okay, is there a way ... So, I know there's probably confidentiality issues here, but if a newborn screening program, which I am from Iowa, wants to look at data from a newborn screening perspective, but we have more than one center in our state, is it possible to get data that shows it from each of the centers in the state?

Alexander: From each of the centers in the state ... Probably brings us to the compliance group and ask if it's allowed. So, like from ... All I can think about right now, I think you could.

Carol Johnson: Okay.

Alexander: But I need to check with compliance.

Carol Johnson: Well, so I guess maybe the background for you, Alex, the reason why I'm asking is that we have two CF centers in the state that prior to the end of September, really were functioning as very independent centers. And so it would be nice to look at that data now from both centers so that we could sit down together now as a more cohesive Iowa CF group and make sure that we're consistent in how we're entering data into the registry.

Alexander: Mm-hmm (affirmative).

Dr. Susanna McC: Hi. This is Susanna. I just have a comment about that. I think it's the two of you ... If both centers requested that it be broken down, that there would be no problem with that. There maybe something to sign, just to verify that for posterity, but certainly the sharing of data between CF centers has been long used for a cystic fibrosis quality improvement initiative. So, I don't see any barriers. I did want to point out that this gets a little bit tricky because we're looking at where centers are located and we do know that some kids are born in one state and get followup care in another state. So, this happens in Illinois, in the Northwest Illinois. A lot of people go up to Madison, Wisconsin for follow up. In southern Illinois, a lot of people go into St. Louis for follow up. I think where your centers are, you get things from central Illinois and eastern Nebraska as well.

Carol Johnson: Right, right.

Dr. Susanna McC: So, there are components of this ... And we do identify it by where the center is, but as making this as a summary of what happens in the state and what happens in the center, there are some flaws in that as well. We have not dug down into how much difference that may make, but frankly I think it's more important to get the diagnostic information standardized a little bit better so that we are comparing apples to apples.

Carol Johnson: Right.

Dr. Susanna McC: Before we start doing things like that, but I think if people wanted to see how much it was affecting their numbers, there would be activities that could take place in order to look at that, even at the level of the centers. So, you might look at ... For the center in Iowa City, so how many of those babies ... What's their median age of diagnosis, but how many of those babies are coming from western Illinois-

Carol Johnson: Right.

Dr. Susanna McC: Or maybe even southern Minnesota, I'm not sure what all the referral patterns are. You know what I mean?

Carol Johnson: Yes, yup.

Dr. Susanna McC: And you could say like, "Okay, what if we look at the only all Iowa babies?"

Carol Johnson: Correct.

Dr. Susanna McC: For those of you who don't know this, state of birth is an entry in the registry. I am hesitant to take on any broader analysis with the current data definition issue. But, I think centers who are working on this with colleagues in the same state and/or state newborn screening programs could easily look at their own data and see what it looks like if they exclude patients who were born elsewhere.

Carol Johnson: Right.

Dr. Susanna McC: We also have, in our own center, we have patients who had delayed diagnoses who were originally referred to a different center as well. So, it may say something about the Illinois screening program over all functioning that it doesn't give us a lot of insight to our own practices.

Carol Johnson: Well, and we certainly have the same issue too, Dr. McColley, where we have Iowa babies that go to Wisconsin, like to the Gunderson clinic in Lacrosse, or they go to Minnesota, or they go to Sioux Falls, South Dakota, or Omaha. So-

Dr. Susanna McC: Right, right. Yeah, I mean, it's not just in your state. It's all-

Carol Johnson: It's everywhere.

Dr. Susanna McC: Phil has called them border babies.

Carol Johnson: Yes, yes. We do too. Thank you for-

Dr. Susanna McC: There are a lot of towns along borders because a lot of borders in the Midwest, especially rivers and things like that ...

Carol Johnson: Right, right.

Well, thank you for answering my question, Alex and Dr. McColley. Appreciate it. Thank you.

Dr. Susanna McC: Sure.

Marci Sontag: So I'd like to read a question that actually came up in the chat box. And this is ... Maybe Alex is already into it. The question was from Kevin Edwards of Nebraska. If the gestational age is taken into account looking at the data? So a baby who was born at 23 weeks has a positive CF newborn screen, maybe even in the NITU, goes through the multiple newborn screening as recommended by CLSI, pulls a positive newborn screen, but the time elapsed from date of birth to a confirmed diagnosis might easily be greater than 60 days until that baby was big enough to actually have a sweat test.

So, I wonder how would you respond Alex? I'm wondering, that would be an easy thing to collect, the gestational age, is to take those babies in and out of the analysis because there might be some bias there. It might be skewing the data.

Alexander: Yup, good suggestion.

Marci Sontag: Yeah.

Foddy: Marci, can you hear me?

Dr. Susanna McC: Yeah, we could limit an analysis to just full term babies defined as ... Well, you could define it several ways. I'd say over 37 weeks given both the sweat test, data, and the whole health issues with late pre-term.

Marci Sontag: Yeah, that's a good suggestion. Thank you Kevin.

Okay, [Foddy 00:54:24] has a question.

Foddy: Can you hear me?

Marci Sontag: I can hear you. You're quiet though, so if you can just speak up a little bit that'd be great.

Foddy: Okay, so I just want to make two points. The slides showed clearly there's a discrepancy between the median age of diagnosis. So the graphs show the median age for the country was around 15 days, but another slide shows that you have the median age for sweat test at 30 days, and median age for clinic at 41 days. I think these slides make a state where we are more old fashioned, we use sweat test as initial diagnosis, makes us look bad because our age of sweat test and clinic visits are very close to each other, but we're reporting them as the age of diagnosis, not the time of completion of newborn screen. So, just making that point.

The other point is the suggested goal of 15 days. I'm not sure where that is coming from or what it's based on, and that leaves us with a really big window between 15 days as a goal, but 60 days as the finisher of late diagnosis. So, what's happening between 15 and 60? Is this all [symptomable 00:55:25]? Because-

Dr. Susanna McC: So, I'll answer that and I will be the first to say it's arbitrary. Remember that it's a goal for a median, and that's really based on, not that this necessarily has a normal distribution, but thinking about the overarching goal that the vast majority of babies are diagnosed by 30 days. But it also comes in ... And again, using data definitions that are extracted as opposed to sort of [inaudible 00:55:59] as some of the ones that we're proposing. We do see a large number of states reporting numbers that way even when we look at diagnosis after seven days of life.

So, it's not ... That goal was set by the leadership of the Cystic Fibrosis Foundation Quality Improvement Committee. There's a little bit of subtext in there because there are members of that group, most, particularly Phil, who are really looking at broadening the genetic panels so that a much higher proportion of kids, especially in states like mine, with high minority racial and ethnic populations, so the vast majority have those two mutations. And I do think, by the way, that a lot of these diagnostic dates, the way they're extracted, are on kids who have two copies of two CF mutations, or homozygote, or something identified on the newborn screening. I know that in our center, and as many people would talk to, we bring those kids in right away.

We try to sweat them, but if they don't have adequate sweats, we begin treatment. And the majority of them will have positive sweat tests. There are some cases in which the spot doesn't tend to match the baby after you do more evaluation and odd things like that. But, I think that's the reason why a lot of states are reporting those late ... I'm sorry. Those early dates. But it's an arbitrary definition. It stems from both what people are reporting and the 30 day for all goal.

Foddy: I think the 30 day goal is realistic. The 15 day goal is not realistic for states that do a screen process. We did a lot of projects locally to decrease our age of diagnosis from 34 to 24 days. And we were very happy that we're within, below the goal to find out that the goal was changed to 15 days, which I think we will never achieve.

Dr. Susanna McC: Yeah, well-

Marci Sontag: I was just going to say to really, when you look at the data, when you say most of the states were making that diagnosis, Susanna, by that date, or 50% ... There's a lot of states who that data was probably not accurate. So, I think once we have some accurate data, using these new definitions, what will they be able to evaluate? What actually is happening in states, and we can look at states who really have good systems in place for timely diagnosis and go, "Okay, here's what the goal really maybe should be." And maybe that's not realistic once we have accurate data and the consistent definitions across states.

Dr. Susanna McC: Yeah, I agree. And I think that really I would focus ... So, if you've got an average that's less than 30 days, and you're getting in 95% of kids diagnosed and initiated treatment by 30 days, that is what we think can really help improve outcomes. Now, of course, there are these data about growth deficits in the first year of life in the newborn screening population, and so there's a hypothesis that earlier treatment could actually change that. But we don't actually know that. And there's some growth factor and other abnormalities that are seen in newborns with CF that might make that not actually true. So, you always like to identify a target. But, you can't always know that that's realistic or even beneficial.

Foddy: Right.

Marci Sontag: So we're approaching the top of the hour. Are there any more clinical questions? Does anybody have a question?

Okay, I know I can speak for myself here, if you have a question that you'd like to talk about please reach out to any of us today. I'd be happy to take questions and I know Alex and Susanna would as well. So, if you think of something later and you say, "I have this ... I didn't really quite understand this." Or, "How did my data get ... How's my state look this way?" Please reach out to us and we will continue this conversation. And I want to just really give a heartfelt thanks to the CF Foundation and to Susanna for your leadership on this. We've been talking about this for the last several years of how to move forward with improving our definitions and our data terms, and I think we're getting there. It's not an easy process to change systems and I appreciate you all being very receptive to this and make taking those steps to make the changes in the registry just as we're doing on the newborn screening side so we can have consistent terms and be comparing apples to apples. So thank you very much.

And Susanna and Alex, also thank you for helping us to answer the questions today and glad you all could join us. So, with that I will end the call. Thank you all for your attention and your great questions and we will talk to you soon.