Marcy: Okay. Again, good morning and welcome. We are very happy to have you all here. We have great attendance, and I anticipate we will have a very good meeting. We are trying a new webinar platform today, and so what we're doing is ... It allows everyone to ask questions in a question and answer box. If you ask that question, I would like to speak. I will try to promote you to a panelist so you can engage in the conversation. We're negotiating how to work through this new software. I appreciate your patience as we do that.

Our agenda for today, we have Dr. Sasha Cornell of the Oregon Health and Science University, Cystic Fibrosis Center. We inadvertently put her on as being from Colorado on the agenda that came out, and I think that is just wishful thinking on our part. We'd love to have Sasha here in Colorado with us but she really is in Oregon and doing a fantastic job there. Dr. Cornell will be talking about the new CFF Diagnostic Guidelines and the impact of those guidelines on newborn screening programs and on laboratories, who are doing newborn screening.

Initially advertised was Carol Johnson from Iowa, who was going to be talking about some of their experiences in quality improvement in newborn screening for CF. Due to circumstances beyond our control, she was unable to join us, and we are very fortunate that Mr. Alex Elbert from the CF Foundation will be presenting today on his preliminary diagnostic outcome data from PortCF.

As you may recall, the CF Foundation, and Alex did a great job a few years ago giving us data from each of the states on their outcomes for diagnosis and time to intervention but that was from 2012 and we've had many requests to get data from 2013 on and he is here today to present his preliminary data and I'll get some feedback. We are very excited about that as well. With that, I am going to stop sharing and hand it over to Sasha. Sasha, you can share your screen.

Sasha Cornell: Okay, I think ... Can everyone see that?

Marcy: Yeah, we can see it just fine.

Sasha Cornell: Okay. I apologize. My camera is over here and my slides are over here. You're going to look at this side of my face. That's okay. Just as an overview, about 64% of new CF diagnoses come from newborn screens. That's why this is such an important topic. They wanted to really tighten down the definition of a diagnosis and give more guidance in terms of how you get there. Sweat testing is still the golden standard for confirmatory testing but sometimes it's not done if two CF

mutations are found on the newborn screen. Despite advances in newborn screening the diagnosis can still remain unclear at the end of the day.

As most of you know, newborn screening in the United States began across the country in 2010 but there's still a large population of unscreened individuals, who remain and who may present with chronic symptoms. The algorithm for newborn screening in particular depends on the state laws and the demographics but most of them include DNA. I can happily say that soon Oregon will be one of those that does include DNA.

The other thing that is important to know is that CFTR2, which is the project that Dr. Sosnay is working on is shedding a lot more light on the physiologic and functional nature of the most common CF mutations, and this has all been since the last published guidelines in 2008. One of the other big issues that they wanted to address with these new guidelines is that there's still a lot of differences between CRMS in the US and CFSPID in Europe. For those of you who don't know what CFSPID means, it's CF Screen Positive, Inconclusive Diagnosis, which actually makes a whole lot more sense than CFTR-related metabolic syndrome, which is what CRMS stands for.

They convened this international committee to develop updated guidelines and there are 32 experts who gathered prior to the 2015 NACFC. They reviewed published guidelines as well as more recent literature since 2008. The executive committee, which was 10 people from four different countries developed statements that were then reviewed by the entire committee, and then everyone voted on them. They had to have 80% affirmative votes for acceptance. If voting against the statement, an individual was asked to revise the statement of the parts that they didn't like or give an explanation for their vote. If there was less than 80% agreement, the statements had to be revised and then resubmitted for voting again.

The agreed upon statements were then presented at ECFS in February of 2016 and then they circulated the draft manuscript and asked for public comments. In the end, they had 28 statements that were voted on and 27 were approved. They covered for overlapping categories with the screen and non-screen populations, newborn screening populations as well as fetuses undergoing prenatal testing, infants with uncertain diagnosis specifically looking at the CRMS/CFSPID and then patients presenting clinically. These are the non-screen populations including home births or regions prior to the implementation of universal newborn screening, false negative screening tests, and older non-screened individuals.

For today, I'm going to focus mostly on the screened population but I just want to show you the simplified algorithm for all populations because it's anything but simple. You can see at the top you enter the algorithm with some clinical presentation in CF for either newborn screening, signs or symptoms, family history. Then you've got chloride testing and they know in the fine print at the

bottom that this is not necessarily in order because obviously for prenatal testing or due to family history, you wouldn't do chloride testing until the baby is born. For the sake of argument for today, you would go to chloride testing. If you were greater than 60, you would be diagnosed with CF. If you were 30 to 59, it would be an intermediate result, and less than or equal to 29 is considered CF unlikely.

The meat of the recommendations are really in that intermediate range because that's where you're going to have the most variability in practice. Once you get an intermediate sweat with a look at genetics and then you would either find two CF-causing mutations or not or maybe somewhere in the middle. That's where some of the physiologic testing comes in looking for other ways to show that CFTR is not functioning correctly. At the end of the day, you either end up with a CF diagnosis, CF diagnosis not resolved or CF unlikely. We'll talk more about each of these.

The one big thing that I will point out now and also at the end is that the sweat chloride ranges have changed. There is no longer a different range for newborns and greater than six months of age. It just [inaudible 08:21] for everybody no matter how old you are. That will simplify things a little bit, but it will also create some confusion for adults who present with intermediate sweats and previously those would have been considered negative.

What does a positive CF newborn screening mean? Well, it depends on what algorithm is being used. There are three main algorithms as we all know, IRT/IRT, IRT/DNA, IRT/IRT/DNA, and there's variations on this but those are the three overarching categories. The DNA panels vary anywhere from 23 to 40 mutations versus actually doing more extensive genetic testing like next-generation sequencing as we've heard other people talk about on this webinar before. Some programs also utilize a very high IRT as a fail-safe for a safety net.

At the end of the day, what the family is told, it depends on which algorithm is used and so there's a wide spectrum of risk for actually having CF [inaudible 09:32] to a positive newborn screen ranging from 1% for the very high IRTs because there can be other things that cause that and up to 100% is you have an IRT/DNA algorithm and you find two CF-causing mutations but they will point out several times in these recommendations that CF newborn screening is not diagnostic. It is still a screening test even if you have two mutations identified.

All positive CF newborn screens must be confirmed with proof of CFTR dysfunction of some sort, whether that be sweat test or some other methods that I'll talk about in a little bit. The other thing that they point out several times is that CFTR gene analysis should be done on DNA obtained directly from the infant even if genome type is reported as part of the newborn screen so that means that even though you might have two CF-causing mutations on the newborn screen, you still have to actually send genetics on the baby after they're born.

This is table one from ... Sorry, I should go back. There are two ... This is actually a part of a series of articles in the supplemental to Journal of Pediatrics that was published this year. Some of this comes from the main article that they published but some of it is from an article specifically looking at the screened population. I put the references on the bottom of each side to tell you which article it's pulling from.

This is table one from the second article which is on the screened population and they just basically pull the specific statements from the main paper that are specific to newborn screening. I actually added on the side column just the percent agreement because it wasn't in this table, in this paper, but it was in the main paper. I thought, it's interesting to see what had a 100% agreement and what actually came close to having to be reworked and revoted on. I find that quite fascinating. These are the statements that are specific to the screened population and I won't go through all of them but basically ... Because we'll talk about some of the more granular detail as we go through the rest of the slides. If you want this for reference, it's there.

I wanted to talk a little bit about sweat testing industry population because they do have some recommendations and guidelines that sweat labs can implement to try to get good quality testing and interpretation. They recommend sweat testing done on all infants with a positive CF newborn screen, family history or prenatal genetic test but they need to be over two kilos, over 36 weeks gestation and it should be done as soon as possible after day 10 and within the neonatal period which is probably less than four weeks of age. It should be done at an accredited lab that follows [inaudible 12:51] guidelines.

Results as I had mentioned greater than 60 is consistent with CF even with a positive sweat and two CF-causing mutations, they should have genetic testing as I mentioned before. In the intermediate range from 30 to 59, that indicates that the patient may have CF. The sweat test should be repeated and if still intermediate, undergo extended CFTR gene analysis and/or CFTR functional analysis. I'll talk more about the intestinal current measurement in the [inaudible 13:26] in just a minute.

CFTR2 should be used to help interpret the sweat results and genetic mutations specifically looking at those mutations with varying clinical consequence because there is a lot of information in CFTR2 that can help you understand what those mutations might be. Then obviously, under 30 millimoles per liter, CF is unlikely but there is caution that you can repeat the sweat if clinical suspicion or family history, et cetera. This causes a lot of consternation for some people but it's important to remember that some mutations are associated with normal sweat chloride levels just to confuse matters more.

There are a lot of challenges with sweat testing in this era. I just highlight some of the issues that people talk about and that they talked about in these guidelines. There are higher rates of [inaudible 14:29] in neonates. They are little

... If they haven't actually had a diagnosis, they may be volume depleted and difficult to get them to sweat but it's still important to do it.

The diagnosis may already seem like it's confirmed to the parents if they found two mutations on the newborn screen and so having to go through a sweat test may cause the parents to think that, oh, well maybe, it's possible that my child doesn't have CF even though they have these two mutations. That can cause some emotional distress. Intermediate sweat test then cause significant confusion for both the family and the PCP.

Then once presumptive CF diagnosis is made, it may be difficult to get the sweat test. Insurance may not think that it's necessary and we may have to do some education around that. Sweat test do not necessarily result in a change in care. It doesn't change what you do with the baby but obviously you still need to do it, and then it also doesn't inform personalized medicine the way that genetics does. New mutations that are potentially eligible for modulator therapy are obviously a perk of having DNA and sweat testing doesn't have that same benefit.

The other issue obviously is technical. It's not available in a lot of places due to cost or equipment and expertise but they emphasize that the foundation really wants you to do it and I'll talk a little bit more about just their mandating it to get the kid into the CFF registry.

Going back to the genetic piece for just a second, CFTR gene analysis on DNA changed directly from instant to ideally be performed as part of the diagnostic evaluation even if a genotype was reported as part of the newborn screen and then I suppose to the question of modulator therapy. In order to be eligible, insurance companies will require DNA directly from the newborn after birth not on the blood spot.

In some cases, we may actually need more in depth genetic analysis so they highlight two uncommon or not uncommon situations but situations where it's standard genetic analysis is really helpful but obviously for R117H, the Poly T status and TG repeats. Also, sometimes, very uncommonly, you can have two CF-causing mutations that are in cis not in trans in which case the sweat would be normal and genetic analysis with parental testing could explain this result and clarify that the infant does in fact not have CF and [inaudible 17:19] from over medicalizing the symptoms.

This is a really important part of the guidelines for me. It helped to clarify a lot of undetermined pieces. The CRMS/CFSPID is reserved for those screening positive infants without clinical features consistent with CF. That is a really key statement. If this child has features of CF, this is not the right diagnosis, and they have to be a screened population. Someone who was not part of newborn screening but presents in some other fashion, then they cannot be diagnosed as

CRMS/CFSPID. They would instead get a diagnosis of CFTR-related disorder which is different.

If you have a positive newborn screen, but the sweat test is intermediate, you would then move to a second sweat test which will either provide clarity or it won't. If it doesn't, then you would get genotyping, extended if necessary, and then also they recommend a clinical evaluation by a CF physician by two months of age. Then repeating the sweat again at six months of age.

Infants who remain asymptomatic but have persistently intermediate sweat test and genetics of less than two CF-causing mutations should be categorized as CRMS/CFSPID and followed appropriately in an accredited CF Center as well as infants who have a positive newborn screening and two CFTR mutations less than one of which is CF-causing.

That's where the mutations of varying clinical consequence come in. Normal sweat chloride levels, they would also be categorized as CRMS/CFSPID. These are the ways that you get this diagnosis. If people have questions, they can ... I don't know, Marcy, if we want to do questions at the end or-

Marcy: I'd hold questions to the end. I think that will be more-

Sasha Cornell: Okay. I adapted this from a table from the appendix. I added this column on the side to say this is ... If you have DNA in your algorithm, these lines are pertinent to your algorithm and if you only do IRT/IRT, then that bottom line is really what you would be looking at. This just helps break it down. If you have no available mutations in the case of Oregon right now, then you can't actually look at those. This tells you where you might get these CRMS/CFSPID diagnoses as well as the more straightforward [inaudible 20:13].

If there is still not clarity, you need to do further functional CFTR testing and there are several ways that you can do this. They talk a lot about ICM and NPD. These are alternative ways to look at CFTR functional capability. NPD can be performed in infants with unclear diagnosis so that it needs very experienced operators but it actually could help you confirm the diagnosis. It's something that if you need to send your patient to a center that does NPDs it would be something to think about.

Then analysis of CFTR function in the intestine may also help confirm CFTR dysfunction with the CFTRs obviously highly expressed in intestinal epithelia. It does again require experienced and skilled personnel. In the United States currently, it's only available on research basis but in Europe, it's used more widespread. Combining the two would also potentially be helpful if you were really struggling to characterize what an infant needs.

Faecal elastase, is obviously another tool at your disposal, is readily available for babies. A result less than 200 micrograms per gram in the absence of diarrhea is

a biomarker of pancreatic insufficiency although the levels fluctuate fairly significantly during the first year of life. For infants who have a [inaudible 21:53] sweat, an elastase may give you a diagnosis of pancreatic insufficiency, which would then allow you to treat the baby appropriately until you can then confirm with a follow-up sweat testing.

Serum trypsinogen is also something that they talk about as a potential biomarker. It is higher in infants with CFSPID, who went on to convert to CF compared to those who remained in the CFSPID group. If there's question about whether an infant has CRMS/CFSPID or whether they are more fitting into an actual CF category, this might be a biomarker you can look at. The other thing is they talk about newborn screening IRT, which is typically lower in the CFSPID infants compared to those who meet CF diagnostic criteria.

There are some other non-specific things that you can look for, specifically, CF respiratory cultures although they are non-specific. Infant PFTs if you have that available at your center and imaging. They specifically point out that the benefit, the risk benefit of chest CT in infants is questionable because based on the Australian data, there doesn't seem to be a lot of obvious pathology on CT yet although in older children there is. In the newborn period, I don't think it would be something I would advocate for.

The bottom line is, in the US, the standard of care is to establish the diagnosis by two to four weeks of age and that includes follow-up evaluations that you need to clarify the diagnosis within that time frame. In this, they talk a little bit about making a presumptive diagnosis in order to not delay initiation of treatment. That's really the big thing that you need to take home from this is that they don't want you to not treat babies if you think that they have CF. Waiting for a confirmatory testing like a sweat test if the baby is not wanting to sweat for you.

The way that you get a presumptive diagnosis of CF is you have a positive newborn screen that reveals two CF-causing mutations. You have a newborn screen based on the [inaudible 24:19] algorithm plus symptoms of CF and specifically growth failure or malabsorption. If you have meconium ileus, regardless of whether you have a positive newborn screen, and also, prenatal testing with two CF-causing mutations in trans, and this would obviously need to be confirmed by parental testing.

They say that the confirmation should proceed as quickly as possible but should not delay treatment. That was something that achieved high agreement from all of the experts. Once the diagnosis is established and confirmed, genetic counseling should be offered and this includes both CF and CRMS/CFSPID infants. I know that that's a tricky thing in the States where there's not a lot of genetic counseling available.

A little bit about the registry changes. Starting in 2017, a sweat test is now required for a new entry into CFFPR. Prenatal diagnoses, they want you to list

the date of presumptive diagnosis as the date of birth, not the date of the genetic testing on the amnio because they want to actually offer timeliness measures. They want to be a little bit more precise and then for presumptive diagnoses, confirmatory sweat testing again should take place as soon as possible and it's considered confirmed if you have a sweat chloride greater than or equal to 60.

If you have CF-causing CFTR mutations identified, and a sweat chloride greater than 30, two variable or uncharacterized CFTR mutations and identified and you have physiologic testing that demonstrates CFTR assumption. If you have two CF-causing mutations identified from a blood specimen that changed directly from the infant then newborn screening is not sufficient or if you have NPD or ICM values typical of CF.

Then diagnosis reclassification in the registry, this would most often occur if you have a CRMS/CFSPID that develops clinical features of CF and you want to recategorize them as actually having CF now instead of CRMS. They want you to note the date of the clinical diagnosis of CF as well as the date of onset of clinical or [inaudible 26:41] that led to the change in the diagnostic category. Their sweat turned positive. The culture Pseudomonas or there are rare cases where a genotype is reclassified as CF-causing.

This is from the main paper but it's a really nice summary if you want to look at it that just compares the 2008 guidelines to the 2015 and then major changes that were made. I won't belabor all of this because we've talked about a lot of it. Then I thought that in the appendix to the screened population paper they have three case studies and I though the third was actually really illustrative of some of the major issues that we see. Marcy, do we have time to just go through this real quick?

A female infant born at 38 weeks gestation with a birth weight of 2.8 kilos, African-American parents. Prenatal screening revealed that the mother had G551D, the father had a 23-mutation panel that was negative. The baby turned out to have a positive CF newborn screen with an elevated IRT and one mutation obviously mom's mutation of G551D. She was followed by her PCP and at two weeks of age, was breastfeeding but the weight had actually decreased to 2.3 kilos so below her birth weight.

They ordered a sweat but she did not sweat. There's two [inaudible 28:21]. At four weeks of age, she was seen again and weighed 2.2 kilos. A repeat sweat at that time was again two [inaudible 28:29]. A third sweat at six weeks was positive or with 89 and 94. She was then seen at the CF Center and was started on enzymes, albuterol and Chest PT. Further testing was completed and her last [inaudible 28:44] was less than 15. She had her mom's mutation obviously on genetic testing as well a rare second disease causing mutation from her father, that was not on the 23 mutation panel. Her slow weight gain was then established during the subsequent visit at the CF Center and her PCP.

At three months of age, she presented with poor feeding, a three-day history of reduced p.o. intake, irritability, no cough or runny nose and over the previous 24 hours she had eaten very little and had had only two wet diapers so worried obviously about dehydration. On physical exam, she is lethargic, tacky membranes, her weight was at the first percentile. No chest findings on exam and her belly was soft. The most likely etiology of the current findings in this infant is what? [inaudible 29:44] malnutrition, acute CF exacerbation, DIOS, or electrolyte abnormalities. Any guesses?

Marcy: I'm going to guess D.

Sasha Cornell: You would be correct. I hope it's not just because you've read the paper. I'm sure it's not. I think the take-home for this is that this infant was very sick and had hyponatremic dehydration. They point out, and this is one of those tricky question things that they do where they don't specifically say that the baby was started on salt supplementation which most CF centers would do because those are the guidelines but in this case, it was not done and so she developed severe electrolyte abnormalities that were causing these behavioral changes and poor feeding.

At any rate, you can read through the description of the risk factors and everything like that but I think the important part ... This highlights the emphasis they put on ... They don't want the confirmatory testing to delay treatment because if this baby had been treated with enzymes with the poor weight gain, and the carriers, at least carrier status, with a [inaudible 31:13] sweat test, multiple [inaudible 31:16] sweat test. I think this episode of dehydration could have been avoided. That's really the point that they want to make. I thought it was a nice case that brings up a lot of different issues in this population. That's all I had.

Marcy: Sasha, thank you so much. That was a great presentation, very informative and I think very helpful for the newborn screening population to hear what ... How those changes will impact the newborn screening systems. Just as you noted the CF Foundation is collecting the information on the time of presumptive diagnosis. We're talking about intervention and starting treatment. At New Steps, we are trying to collect that as well because that's really the [inaudible 32:04] information is, when do we first get some intervention started for this child and then perform the diagnosis and some [inaudible 32:13] after that.

George Rich [inaudible 32:15] have a comment and George, I promoted you to a panelist and hopefully, you'll be able to talk with us if you unmute your cell. Okay, George, I'm not hearing you so I think you should be unmuted. George, are you there? Okay, I'm not hearing George. The comment, and George please interrupt if you can get access to the speaking but his comment was related to NPDs and that NPDs are not available readily at every CF Center and within every state.

Those are only available at those centers who can really do them for research purposes now and some are doing them for the diagnostic purposes for newborn screening although I think it's pretty rarely used. It's in there as an option but I think it's pretty rarely used for the newborn screening population. For those of you who are out there in the newborn screening world who aren't familiar with NPDs, they really are a very specialized test that it's only really a handful of CF Centers of the research level grade [inaudible 33:26].

If any of you have questions specifically for Sasha or related to these diagnostic guidelines, you can type them in the Q&A box at the bottom of the screen and I'd be happy to see if we can find the answers for those. If not, I see a chat. Let me see. What is considered intervention? The question is changing formula to address weight issues or administering medication. Sasha, do you want to start with that?

Sasha Cornell: Well, I guess it would depend on the situation. To my mind, the downside of ... If a baby is not gaining weight and has malabsorptive stools and you can't confirm the diagnosis yet, I have sometimes empirically started kids on enzymes because the downside is fairly minimal. Obviously, a baby who was not quite as severe, it might not warrant an empiric trial on an enzyme replacement.

Marcy: Yeah. We worked very closely with this. Many CF conditions come at [inaudible 34:46] to [inaudible 34:47] as well as the CF newborn screening community. I feel like some guidelines that it's really, based on what is needed for that child. If someone has taken a look at that child and decided here's an intervention that needs to be started or maybe an intervention does not and it may be something as simple as starting salt of enzymes, or maybe the decision to say, "You know, this baby is doing okay. We don't need to start salt or enzymes," but that's also an intervention was made on behalf of the child's to either intervene or not.

Sasha Cornell: The other thing I'll say, Marcy is that it really I think ... It is important for that person deciding on the intervention to be a CF physician because I can't tell you how many times, and this is no offense to PCPs but they don't recognize the same things that we do because we see this all the time. Malabsorptive stools, their PCPs have described them to me as, oh, they're okay or the parents will describe them as being okay and normal because they have no idea what malabsorptive stools look like. Particularly, if it's a first baby for a couple. I think it's just important to emphasize that when we get these uncertain cases that it does need to be a CF physician at a center that has experience with this and can make the right decision for that baby.

Marcy: Excellent point. Andy asked a question. Andy, I promoted you to a panelist and you could ask your question live if you can get on. Andy, I just unmuted you. I think you might be on the phone as well. Andy, you had a question about mutation testing from wet sample and I'm not entirely sure what the question

was there. If you want to give us a little more detail that would be great. I think you could maybe mute your phone and get on a-

Andy: Does it work now?

Marcy: That works perfectly.

Andy: I would like some focus or clarity regarding the origin from which we should do a mutation testing because there needs to be a focus and I still think that it's a difference between one and two screen states because I think the issue is revolving that a diagnostic test has to be from an independent specimen. If I understand these criteria or at least the interpretation correctly, these would mean change for a lot of newborn screening programs.

Sasha Cornell: Sorry, I can't hear that at all.

Andy: I will type it.

Marcy: Okay.

Sasha Cornell: Okay.

Marcy: I think the question was related to which sample are you doing the genetic testing from. If you do the genetic testing, on the second sample on two screen states, they have repeated or a persistent [inaudible 38:13] and then the mutations on that second sample. You have two different samples from the baby and the human baby has CF. Then you do a sweat test to confirm. I think having had previous conversations with Andy about this diagnostic challenge, I'm guessing that's what he's talking about but we'll let him type and ask.

Sasha Cornell: He said, "You're correct."

Marcy: Yes, okay. I think Andy that the way I interpret the guidelines, and someone else, please chime in if I am not correct there, is that, if you have a second test on that individual, a sweat test, the diagnosis is confirmed. However, if you're going to enroll that child in any of the clinical side in any of the trials or for any of the therapies that are specific to those mutations, you would have to repeat that mutation analysis to make sure that that was correct. That's beyond the scope of the diagnosis. That's for additional treatment and therapy.

Along that line, Jerry and Joy asked, since we need to repeat testing for CF genetic mutations, even if two mutations are identified via newborn screening. What testing is recommended just between the identified or a more extensive panel?

Sasha Cornell: Well, they don't specify and I would leave that up to the discussion of the clinician ordering the test. It is expensive to get genetic testing and we often will

do a targeted screen when we know that it's ... If we know the parent's genetics or a sibling's genetics. Then we'll have our lab run a more targeted screen. We recently had a case where we had two siblings and both had a rare mutation ... One rare mutation that was only identified on full sequencing. One child had insurance, the other child did not for reasons I won't get into.

We ran full sequencing on the child who had insurance to get the diagnosis or to get the second mutation and then confirmed it with a very limited sequencing looking for that specific gene in the sibling. It would depend on the situation and what information you had that might limit the scope of what the laboratory might do.

Marcy: Yeah, and then additional confirmation on this discussion is that the newborn screening genotype is not considered a diagnostic genotype. That's what [inaudible 41:00] who's one of leaders of that [inaudible 41:03] diagnostic.

Sasha Cornell: Yes. They say that over and over and over again in the papers.

Marcy: That's true for all of newborn screening. Newborn screening is never diagnostic. It is a screen. It should never be considered diagnostic and you need to actually see the [inaudible 41:18] assess that baby. Finally, I'm just going to read Susana McCauley's comments and then I want to move on and make sure Alex Elbert has enough time to ask his questions as well.

Susana said, "NPD seems to be more commonly used in Europe for diagnostic conformation than it is here in the United States, an issue of two mutations on the [inaudible 41:39] is there is up to 5% rate of misclassification in newborn screening programs. I think that rate might be a little higher then it's typically seen but that might be the extreme. If there are two mutations, someone probably has CF but rarely it is not the baby who presents to you. Thank you for that comment as well, Susana.

The final question was, do we have a cut off? This is from Jay [inaudible 42:07] as well. Do we have a cut off for serum trypsinogen level to identify patients with CRMS with higher risk to have CF and I would say we don't have that information yet. It really is quite variable. IRT in itself is variable and quite variable in those specific patients. With that, I want to say thank you so much, Sasha. That was a great-

Sasha Cornell: Welcome.

Marcy: A good discussion on that presentation so thank you all of you who asked questions. I'd like to hand it over to Alex Elbert, who's going to give us a brief update on what's happening at the CF Foundation with [inaudible 42:42]. Alex wants to show your screen. Alex said he only needs 10 or 15 minutes so hopefully this will be perfect and if not, we'll definitely invite Alex back for another session if [inaudible 42:54] needed.

Alex: Good afternoon. Thank you Marcy. Can you hear me?

Marcy: We can hear you just fine.

Alex: Okay, can you see my screen?

Marcy: We can't. Do you mind putting it in presentation mode.

Alex: Of course.

Marcy: We see-

Alex: This is better?

Marcy: That is perfect.

Alex: Thank you for inviting me to speak on this webinar. For those who doesn't know me, I'm Director of the Patient Registry. I'm here with the foundation since 2008. Initially, I was tasked for this transition in [inaudible 43:30] registry like [inaudible 43:31] would have registry. That is a new platform. I was behind design in manuscript of course is a help from the commercial and subject matter expert. I'm also behind the annual reports on my team. I ran behind in your report since 2011.

We are also responsible for producing center specific reports. Some of you will receive shortly. I'm also helping with different data analysis. For instance, the international comparison of US and UK registry data. Adjusting seasonality and intervals between encounter so like I sent last year or several years ago, I was helping Susana McCauley with her analysis of the newborn screen data.

Today, I will be presenting some data and thoughts about 2013-2016 on newborn screening data in the registry. It's interesting [inaudible 44:33] because right now we are working on 2016 data. All preliminary data analysis there I'm doing and then I'm pushing it to our statisticians who are doing [inaudible 44:42] first analysis of the data.

Let's move ahead and here I'll start with this big table, general summary. As you can see in the column 2010-2012, I was trying to come ... To extract data from that period of time and compare it with 2015 to 2016 data and because like I say [inaudible 45:08] different number of years, in some cases I was putting in parenthesis the average number per year.

Here are from 2010 to 2012 covers three years and 2015 to 2016 for ... As you can see, some of them probably are not of interest to you like [inaudible 45:25]. Probably decreased total number of bars as you can see is decreasing like I would say by 10% or more. The number of patients with CF is decreasing as well.

Number of CRMS case is identified again. Averaging by year is decreasing which I thought is surprising.

You have to have disorder. As you can see I put extra like question mark here because it's impossible to have safety on disorder like in newborn kids, children. Why does this still have that. Here diagnosed by newborn screening. That's another surprising number because in 2013-2016, per year we have smaller number. Prenatal diagnosis, we have [inaudible 46:17] like patients in the recent years. Talk a little bit about this particular variable later.

Date of diagnosis is before date of birth. Again, they have more people in their recent years. State of birth cannot be determined. Smaller numbers but still we have some of those. CF diagnosis after false negative newborn screening results. Here we have a very large. Perhaps I don't know why is this so but we can help meet. [inaudible 46:53] variables that I decided to add to this table. It's age at diagnosis is between zero and 7 days.

We are capturing right now only a single diagnosis date in the registry. We know that it's pretty unlikely that CF diagnosis could be confirmed at the age less than seven. Then I was trying to compare ... Select some states for which median age and diagnosis is very different if you would include patients with diagnosis made after one day at one day or more and median if age is a diagnosis more than zero.

Basically, it includes those performed diagnosis was equal date of birth and those perform diagnosis was made later. As you can see, differences could be quite large especially in cases Connecticut. We have median diagnosis age at 7.5 days but if you would include all patients for where diagnosed at date of birth, it would be wrong. That means that most of the patients were assigned a diagnosis date equals date of birth.

In the middle, I pull another median. In this case, if age at diagnosis was seven days or more, and there's always numbers as well. As you can see, difference could be quite large as well like for North Carolina, like for some other states. Can they explain also differences and that's right to take a look what is going on. I think when we are talking about age in diagnosis about other variables that are difficult to explain from the medical perspective, sometimes we need to go back to the forms and see how we capture the data.

In this case, this is a diagnosis, a current diagnosis for ... [inaudible 48:58] capture patient diagnosis. As you can see, we can capture diagnosis not on this year but we can capture CFSPID or CRMS or it can capture if there are disorder. We usually have this big fields that consist from different multi select choices. That could be select the simultaneous together. Here I need to criticize problem myself in the first round because I was again behind this form. I was trying to cut it from the previous registry, online registry that we had.

These are really clearly understanding of how and what we should capture. As you can see, here on my points about this forms that could be fixed, here I'm giving an example of DNA analysis. They capturing computations in a different place or probably shouldn't be here. We are asking about newborn neonatal screening because we can see it's choice number 15. It's mixed with other variables so that probably shouldn't we even check that newborn screening, right?

In fertility, like the CB, ABD. All these things are coming later. We are mixing all different symptoms at the same time and perhaps it would be better if you would be capturing data in the different way. Here it's just one of the samples how we are thinking about changing diagnosis, capturing diagnosis. For instance, at the beginning we are thinking that we can select the main [inaudible 50:44] that was used for diagnosis of cystic fibrosis.

In this case, we can say to the post prenatal screening or newborn screening for community station. It would be a clear cut separation of entries. Then we can select diagnosis so date of diagnosis. Then the real specific questions then depending on the choice to the first question, diagnosis was made by. Could be made is enabled or disabled. Here I am highlighting let's say prenatal screening is selected. They can include prenatal procedures and symptoms. How was it done by amnio, CBC, or perhaps meconium ileus during ultrasound. For a newborn screening, we can select maybe IRT/IRT method or IRT/DNA or IRT/IRT/DNA, et cetera.

As you can see in diagnosis criteria that recently were published, I think there is a talk about ... I think Sasha mentioned presumptive diagnosis and real diagnosis, confirmed diagnosis. I called them preliminary and confirmed diagnosis dates. Perhaps they should capture two diagnosis dates in the registry. Again, I'm looking for feedback from the community in this case.

Here I added two charts. One chart is from other article that I got from Marcy and Susana. It's about what I was doing to data analysis. It's kind of ... What was I saying? Number of infant studies. CF reported the CF [inaudible 32:23] patient registry born 2010-2012. Same thing for 2013-2016. As you can see, trends has a same biggest states has the biggest number of burst. Of course, remains California, Texas, Ohio, New York. Is that kind of shifting back and forth but trends are pretty much the same.

Another chart, I was trying to mirror what was done in the previous analysis compareing states with different technique for diagnosis. As you can see, states like on the first top chart, states using [inaudible 53:09] DNA are shown in blue. They have definitely much shorter like an average. Shorter past is a diagnosis.

The same is happening right now, 2013 to 2016. However, amongst positive changes, this is at median for combined age. Diagnosis is actually decreasing. It actually approaching the goal. It's 16 years right now and then previous lesson

the growth [inaudible 53:39]. At this point, I guess I can stop. We've got five minutes until the end of the meeting and I will be ... We'll have to answer the questions.

Marcy: Thank you so much. That was very informative and I really appreciate you tackling this data again for us so we can start to look and think of how we have changed. You brought up a question early on about the increase in false negatives that you had noted on one of your first slides. I suspect that is just because we're getting better at a reporting those false negative.

I'd love to hear if others have different opinions on that but I don't think we're probably missing you. I think we're just probably better at identifying them and reporting them back to you. There are some questions. Clement Ren said, "Are the diagnoses you listed on the first table what the centers are entering? We know the CF Centers are inaccurately classifying CRMS. This will also explain how CFTR related disorder ended up in there. Have you done the analysis using CFF definitions of CF and CRMS?"

Alex: Great question, Clement. Definitely we'll include in our derived variables or variables that we calculate. Analytical diagnosis, diagnosis is [inaudible 55:03] created using definitions from the newest diagnostic criteria. We will compare what we have here is what we will receive.

Marcy: Excellent. Clement also says that he likes the proposed changes to the diagnosis page. It will make it easier to identify those who are diagnosed my newborn screening. I do as well. I think that it makes it very clear and it's easy not to see how people have ... If you've misentered that in the past or just not 15th on the list.

Alex: Yeah, it's the problem, they will be, how can we infer it? What with the capturing and what with those new definitions. We always needed to align our previous data entrees. There's a current data entrees without losing the information. This will be the challenge.

Marcy: Yeah. Susana McCauley asked, "What was the age range for patients diagnosed after false negative newborn screen?" We would expect this to go up overtime as patients are ascertained after the first year of life if older kids are reported. Do you have that information?

Alex: No, but this is an interesting question. Susana can contact me after that. I may take a look at it later.

Marcy: Okay, yeah. The question ... I've had a couple of people ask if the slides can be shared. I will get permission from the chief presenters to share the slides and with their permission we will also post this recording on the New Steps website. If you wanted to go back and listen again to the presentations or see the slides, you can do that.

Susana says, "Great presentation." We've had several comments of great presentation so thank you to both of our presenters today for these great presentations. I am not seeing any other question or comments. Alex and Sasha, do you have anything you'd like to add at the end? All right. Well, thank you both for great presentations today. We really appreciate you taking the time to present with us.

Alex, jumping in at the last minute, that was fantastic. We look forward to digging a little bit more into the Cystic Fibrosis Foundation data as well. Thank you all for your time today and we will post these slides and look forward to seeing you again for our webinar that we will have again in two months in the month of July. Thank you so much.

Sasha Cornell: Thanks [inaudible 57:44].

Alex: Thank you, bye.