NewSTEPs

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CPT-1a Update from Alaska

Presentations: Marie Burlette from the Connecticut NBS program

Dr. David Koeller, Metabolic Geneticist

Dr. Matthew Hirschfeld, MCH Director, Alaska Native Medical Center

Sara Denniston from the Oregon NBS program

Sabra Anckner and Jessie Doherty from the Alaska NBS program

Please direct all comments/questions pertaining to this presentation to Sikha Singh at sikha.singh@aphl.org or 240-485-2726

Thalia:	Thank you everyone for joining our call today. Right now I'm going to mute all the phone lines and then after that Carol will take over with the introductions and speakers. Just a reminder to do *7 when it's your turn to speak. I'm going to mute the phone lines.
Audio File:	The conference has been muted.
Thalia:	Okay. Go ahead and take it away, Carol.
Carol Johnson:	This is Carol Johnson, I am the Co-Chair of the Short Term Follow Up Work Group, and today we are very happy to have with us, Marie Burlette from the state of Connecticut's Short Term Follow Up program, and she's going to tell us a little bit more about Connecticut and then we have a robust speaker list about the CPT1A variant. We have Dr. David Koeller, the metabolic geneticist for the Oregon and Alaska programs. Dr. Matthew Hirschfeld, the maternal and child health services director at the Alaskan Native Medical Center. Sara Denniston

from the Oregon Newborn Screening Program. Sabra Anckner from the Alaskan Newborn Screening Program. And Jessie Daugherty from the Alaskan Newborn Screening Program.

I'd like to thank you for joining us today. I hope that you've all survived Daylight Savings Time. Those that observe Daylight Savings Time. And I will turn it over now to Marie, for our state profile for Connecticut. Thank you.

Marie: Hi, thank you. Can you hear me?

Thalia: We can, thanks Marie.

Marie: Okay, hi. This is Marie Burlette and I am the supervising nurse consultant for the Newborn Screening Follow-up Program and it's a short term follow-up unit. And I also have Adrian Manning on the line with me. She's our division director for Newborn Screening. She took the position a few months ago. So she's been with us, here in Connecticut, in the state laboratory for a long time. Actually much longer than I have.

You can go ahead and hit the slide. Just briefly, and I apologize because some of my slides got cut off. So we're missing some things on there like PKU. I'm sorry ... No I think we've got PKU. Anyway, I just wanted to show you just a general timeline. We're currently testing for 64 disorders, the newest that we added was ALD, and I'll talk a little bit more about that later. We have here, in the follow-up unit, we have three nurse consultants. That's including myself and administrative assistant. We're actually located in the state laboratory, which really works very well for us. You can go to the next slide, please.

So, in 2015, we had over 37,600 births in the state of Connecticut. As you can see from my notes, six died. One of those did not have a newborn screening waiver on file. We do ask any parents, including parents of infants who have [inaudible 00:03:09] early on, to sign a waiver if they do not want their baby tested. Right now in Connecticut, the only exception to the newborn screening testing are religious exceptions. So they do sign ... Generally will sign the religious waiver for us. Although I know some of the nurses in some of the birth hospitals are somewhat reluctant to approach parents of ... Understandably, parents of infants who have died.

So we had a total eligible, for screening, of 37,647. Of those, we screened over 99% of infants. Actually, 99.9% of infants. So, we're very proud of that rate. For the total eligible screened in this state, and out of state, that number actually has a typo. That should read 37,614 because two infants were screened out of state. We had 12 refusals where we had waivers signed, and then another 10 ... They were all home births that we were unable to connect with and had no waiver on file. One of the things that we are working on is to work with our nurse midwife centers and organizations to ... First of all, have them stress the importance of newborn screening with the parents. But also if the parents do

decline, to have them get a waiver on file. So it is state law that we need that waiver. Then go ahead to the next screen.

On the next three screens, I've got confirmed cases in 2015. I don't think there's any surprises here. Can you go to the next slide please?

Okay. Our hemoglobin disease confirmed cases ... Those actually, we still have a number of outstanding cases for 215. Sometimes they'll take a while to get a diagnosis for that. But it's not surprising that sickle cell and hemoglobin SC disease top the list. You can go ahead to the next slide.

Okay, and then the next slide that we're coming up to are actually the cases that we've picked up ... Other conditions that we've picked up along the way in current ... Including carrier conditions. And a couple I thought were really interesting here, was the congenital [inaudible 00:05:39]. Actually I was looking that up and that's got an instance rate of one in ten million according to the NIA. Another pretty rare condition that we were able to ... That was picked up as a result of an abnormal newborn screening, was [inaudible 00:05:58]. And that, I don't have the incident rate at my fingertips, but that is also a very very rare disease. So we're happy that we were able to pick those up. My understanding is both can be quite debilitating. Go to the next screen.

What we find most exciting here, at the newborn screening lab, is that we have started XALD screening. We started validating our methods on October 1, 2015. And actually went live with it on July 1, 2016. During validation, we screened every newborn screening specimen that arrived in the lab on October 1st and after in 2015. For a total of 52,757 specimens screened to date. Actually during our validation, we actually had our first confirmed case of ALD. We picked up a boy, we refer to [inaudible 00:07:13] as is our protocol. And they were able to confirm XALD. They also did some ... They also asked us to check the blood spot, or to do some testing on the blood spot of a male sibling of this child. And that child also ended up confirming the XALD. I believe he was two or three years old.

What we've been doing, when we do have a positive screen ... If we have a borderline screen, what we do ask is that they repeat the newborn screening. But for a presumptive positive screen, we also ask if there are any siblings. And generally, if we have the blood spot specimen for the siblings, we'll go ahead and test those. We also make the geneticist aware of the names and the gender of the siblings.

So since that time where we picked up those two boys, the siblings, we've had actually three females who have confirmed with ALD. And we've had ... I'm sorry that was in 2016. Another three males, and that includes another sibling of one of the ... Presumptive positive cases ... That confirmed for XALD. And we had one female that did not confirm. So that is our only false positive that we've had so far, with anything that has fallen in the presumptive positive range.

And then this year, we had a baby that one of the geneticists was already involved with and strongly suspected [inaudible 00:09:00], and at the same time he was calling us to find out about that the baby was flagging for ALD. We were able to conduct that case. We've got another presumptive positive that's pending a diagnosis. That's actually two, one female and one male.

At this point, I'm going to open it up to any questions you might have. Our contact information is here. You can feel free to give us a call or email us with any questions you have. I know a lot of people are starting implementation of ALD screening.

Thalia: Yeah, absolutely. Thank you Marie. I didn't ... That's great. You're right, you're one of the few states that is actually promoting that screening. I think we'll go ahead and hold questions until the end. But feel free to write them down and ask them when we get through with the major presentation here today.

So, I'm going to go ahead go to the first slide. I don't know who's speaking first. Who wants to get the ball rolling here? I think if I go through the [crosstalk 00:10:09].

Sabra: I can just introduce everyone real quick, if you want to go back to that slide.

Thalia: Sure. Okay, sure. Thank you.

Sabra: So, hi everyone. Thanks for having us. I just wanted to introduce the folks that you're going to be hearing from today. So, Dr. Matt Hirschfeld, who is sitting in my office so let us know if you can't hear him, is the maternal child health services director at the Alaskan Native Medical Center. Dr. Dave Koeller, found in Oregon, and is the professor of Molecular Medical Genetics and Pediatrics down at OHSU. Sarah Denniston is our follow-up coordinator that we work real closely with as we do use the North West regional screening laboratory for our testing. Myself, and the nurse consultant for newborn screening for the state of Alaska. Then Jessie Doherty, who is our research analyst and GIS guru who has really helped us with figuring out what things look like.

So, with that I will turn it over to Dr. Koeller. If you want to [inaudible 00:11:10].

Thalia: Dave, don't forget to do *7 to unmute yourself.

Dave Koeller: Am I unmuted now Thalia?

Thalia: You are, thank you Dave.

Dave Koeller: Okay and can people hear me? Okay.

Thalia: Yes, we can hear you fine.

Dave Koeller: Okay, fine well thanks. Let me just go ahead and I'm ... Sabra mentioned I'm going to just do some background information. Try to get people up to speed on this. This is a project that ... Well Thalia was involved with, back when she was in Alaska many years ago. Dr. Hirschfeld and I have been involved with for going on about ten years now. Here's the next slide, please.

So, just a general background. So, Carnitine Palmitoyl Transferase 1A or CPT1A is the enzyme ... Gene that we're going to talk about today. This is one of the enzymes that's required for long chain fatty acid oxidation in ketone production. A deficiency of this is identified by newborn screening. The reason there's concern is that kids like those with [inaudible 00:12:17] another fatty acid oxidation disorder, are at risk for low blood sugars and associated seizures and liver problems due to their inability to burn fats while fasting.

By newborn screening, typically the disorders associated with an elevated ratio of the C0, or free carnitine, to the sum of the C16 and 18 carnitine. The basis for that is that this enzyme actually is required for forming long chain acylcarnitine. So the C16 and C18 are the products of CPT1A, and so if those are low when the enzyme is deficient, then the free carnitine will be high. And it's a genetic disorder that's inherited as an autosomal recessive. Next slide.

So, starting in about 2004, which was when we began expanded screening for Alaska ... I should mention the screening is done by the lab in Oregon as part of the North West Regional Program. We started finding kids out of Alaska that were having newborn screenings that suggested CPT1A deficiency. At this point in time, there was only about 20 or 30 cases actually reported in the literature. When we started seeing these kids, it seemed a bit unusual. But nonetheless, we pursued these as we were doing other fatty acid oxidation disorders with skin biopsies and enzyme studies and those showed that in all these kids, there was a significant reduction of enzyme function. But what was unusual, in particular, was that when DNA sequencing was done they were all found to carry two copies of a single nucleotide change in the gene. The other thing was that looking back at the newborn screening cards for all these kids, the parent had indicated that they were of Alaska native heritage.

So we continued the screening over the next three years with more than 50 cases detected. As I mentioned, there had been far fewer than that reported throughout the world by this point in time. There was also things going on that made us suspicious that we weren't in fact even capturing all these kids. For instance, kids that had a third screen for some reason, because of abnormal thyroid and then they happened to show up with an abnormal screening for CPT1A as they were getting older. Next slide please.

So based on that, I worked with the state and with the Oregon program and some other colleagues at Oregon Health Science University. We did a quality assessment to really test the sensitivity of the newborn screening assay to pick up kids with two copies of this gene. So that happened in 2008. As indicated

here, we looked at approximately 3,000 newborn screening cards by both DNA and MSS [inaudible 00:15:19] analysis. Of those, there was 18 that were positive by a standard newborn screen and 173 that were positive by DNA. So, clearly we were missing a lot of these kids and picking up only about 10% of them. Next slide.

This map just shows a description of where these kids were coming from. This is all, and continues to be, all Alaskan Native babies where we were finding this. And statewide, we were finding that about 25% of Alaskan Native infants were homozygous and another 35% were carriers. If we look specifically in northern ... In western Alaska, which you can see on the map is the areas with the orange and the green, 50% of these kids were homozygous. Another 47% were carriers. Based on this, the gene frequency was 0.7, meaning that this is actually a normal or wild type form of the gene in this region ... Within this population. The other significant point was that this gene was in Hardy-Weinberg equilibrium, meaning that it's been there and it's stable within this population.

What the map shows, is there's orange and green circles. The orange circles ... The size correlates with the relative frequency of homozygous infants. For the green, it's the relative frequency of both homozygous and heterozygous. Really the take home message here is that this is found in the northern and western parts of Alaska. Where we find that the [inaudible 00:17:02] Alaskan Native people reside. Next slide.

This shows actually a map that ... Of the world of course, but it's a polar view looking down from the North Pole. I don't have a pointer but what I would just point out is that where we find this gene distributed, as I mentioned in the western and northern parts of Alaska. Now if you head sort of counter-clockwise through Canada, along the northern parts of Canada, and then along the coast of Greenland ... Where the Canadian and Greenland Inuit people live, it's also very high prevalent. And then also, across the Bering Sea from Alaska, in Siberia within the indigenous population there, the variant is also highly prevalent. Next slide.

So, to summarize what we know at this point is that about half of the Alaskan Native kids ... Born in western and northern Alaska, are homozygous for this genetic variant. We've done a variety of studies over the years ... Which for the sake of time, I don't have any details about. But what we have observed is that kids with two copies of this gene have definitely an impaired ability to burn fat and to generate ketones. This was based on actual impatient fasting studies. There was also an increased risk of hypoglycemia with these kids. Then we have done some epidemiologic studies and we've determined that there's in fact an increased risk of infant mortality associated with having two copies of this gene. In particular, these kids seem to be more vulnerable to die from infectious diseases. Particularly pneumonias.

Now based on this information and what we know about things such as [inaudible 00:18:55], is the idea is ... The assumption is that if we can find these kids and educate parents and practitioners about the risks that we could reduce some of the excess infant mortality that's found in the same regions of Alaska where this gene is. I didn't mention, but in this same part of Alaska, the infant mortality rate is approximately double what it is in rest of the states. The problem is, as I pointed out, is that MSS or [inaudible 00:19:26] screening is not a very good method with only about 10 to 20% ascertainment. Next slide.

This is just a diagram that shows the data from the assessment we did in 2008 to demonstrate the difficulty with newborn screening. So the colored regions that are shaded in that figure correspond to the three genotypes that was homozygous for the variant, heterozygous or with no copies, and then the blue lines ... Horizontal lines correspond to what we would find with different cutoff levels for the C0 over C16 plus 18 ratio. And as you can see, a ratio of 100, which is where we initially had started based on some published reports of ratios that were sensitive, only picks up a small fraction and that was like the 10% or so we were getting. You know, we could lower that ratio and you can see if we lowered it let's say down to 20, then we would get all of those homozygous infants. But we have a very large number of heterozygous and we even have kids with no copies. So really there was no place where that simple ratio could be used. Next slide please.

So I actually worked with Dr. [inaudible 00:20:48] at Mayo with the Region 4 group. We used their tools with the entire data set from those 3,000 infants to try to see if we could come up with a better way to screen. Just based on the tandem mass data. And the conclusion was, we really couldn't do this and that at some point along the way, you would have to report ... Resort to DNA. So the next slide.

So then in July of this year, actually it was July of 2016. My mistake. Alaska actually initiated universal DNA-based screening for the CPT1 Arctic variant. To be clear, what I mean by universal, it's all babies born in Alaska. There's no restriction based on geography or ethnic background.

And that is it for me. I think Sarah you're on deck here.

Sara Okay, can you hear me?

Thalia: We can. Thank you Sarah.

Sara Okay. So, I'm going to take it from the lab point. I'm Sara Denniston at the Oregon State newborn screening lab. We're also the regional program. So in February of 2016, we started our validation and then July 1st of 2016 we started CPT1A DNA and [inaudible 00:22:10] for all Alaska babies. So it's convenient. It's our existing PCR machines we were using for [inaudible 00:22:16]. So it's one punch and one extraction per baby. We're doing about a plate a day, plus a

repeat plate. This is actually a copy of just what the lab brings me and after several trials of what I report to Alaska, this tends to be the easiest way to just to give them the list of lab numbers that are heterozygous for the day and homozygous for the day. Because then Alaskan newborn screening processes those. Next slide.

This is just a copy of what it looks like when we have a heterozygous results. We wanted it to look normal, we didn't want to flag it abnormal in any way just because they're a carrier. Sabra or Dr. Hirschfeld might talk more about that later. We also went through the several variations of how it reads on the report as far as the [inaudible 00:23:09] result. The disorder evaluation. And the note at the bottom was added later, after we started getting many phone calls regarding the new results. Next slide.

This is how our report looks now as a homozygous. So it is in bold at the bottom. There is an attached letter that goes with it. If you want to go to the next slide.

So this is just from our merge database. As you can see our [inaudible 00:23:39] field is up on the top. It's pretty basic. It goes to the provider and I don't know if they in turn send it on to the family. But it does talk about a DVD that Alaska processes and send out to the families. I know that we try to, or Alaska tries to make note that it's detected. We don't want to call it abnormal. This has also gone through several variations over the years as far as just what we want to report to the provider so they have some education. Next slide.

And I'll let Sabra take over here to talk more about what Alaska does with all of this info.

Sabra: Okay. So thank you Sarah and Dr. Koeller. If we could go to the next slide please.

So I just wanted to show ... This sort of mirrors what Dr. Koeller and Dr. Hirschfeld found in 2008. So for our first 152 homozygous kids that we got once started DNA testing, we found that 8.5% of them on the first screen also came up on the [inaudible 00:25:01]. We are a two screen state, so we got another 16% of them on that second screen. So overall we only would have caught about 25% of the kids and we go more than 90% earlier, or at all, than we would have if we were just doing the one screen. The other thing is that Oregon had greatly reduced the reporting cutoff for this particular value, which was resulting in the occasional false positive. Including four other states that Oregon also covers. After we felt confident about this process, then they did raise those cutoff back to a sort of a ... More like what other states are using for this particular value. So about 90 for the first screen and about 150 on the second screen.

As Sarah mentioned, that's created a bit of confusion for some of our providers. We do have a lot of turnover up here. A lot of local [inaudible 00:26:03] who aren't necessarily familiar with what this is in the first place. So that's why we

added that statement to the bottom of our report pages to please call me if you have any questions about it. That you're going to see fewer kids that come up on that mass spec but that has absolutely no relation to this status as a homozygous kid. That the DNA test on the first screen is definitive, regardless of what they're showing up with on mass spec. So that's sort of been an ongoing process that we're working with and making sure that our providers are all educated with that information. We had a couple of providers that were calling them false positives when the mass spec results were normal. So we've been working on that. Next screen please.

So, in our first six months of testing out of about 5,500 births for all Alaska children and about 1,500 were Alaska Native, we had 394 homozygous kids, 556 heterozygous. Which means 950 infants with one or two copies of this variant. Which puts us at 25% of all homozygous kids and 37.5% are heterozygous. So, as you can see that's about 18% of all Alaskan infants are either homozygous or heterozygous for the variant. Which means that Oregon follow-up staff is doing a lot of work because those all get coded and have to be addressed. When the number for most programs is 1 in 800 or so are true positive, we're more at 18 of 100. So we do not report the heterozygous out as anything other than normal. But we are tracking it. So, next slide.

So, Jessie, if you want to explain the maps.

Jessie: Yeah, so we're looking at the homozygous incidence by region. Which is based on the mother's reported zip code at the delivery date. As expected, we do see quite a lot in the YK region, which is 62% and 53% in Norton Sound. There is a little bit more in Bristol Bay, North Slope, and the Northwest Arctic. Just because people do tend to move around. If we move on to ... No actually, what we want to look at too, is because it's on the coast side, we kind of recognize that the expected regions do continue to eat the traditional diet. Which sea [inaudible 00:28:43]. Then as people do move around, we do have a bit of a bump in a few of the other regions as well. So, we can go to the next slide.

The incidence by region for both homozygous and heterozygous was pretty interesting. For YK and Norton Sound, we were above 95%. So almost all the babies born in those regions ended up with at least one of two copies of the gene. Which was surprising. And then in the [inaudible 00:29:13] area, again with the moving around, for 58%. [inaudible 00:29:18] had 50. And then interior, quite a large area, with 37% though too. And then I'm done.

Sabra: Okay, so what we do for families ... So this is unique to what anybody's doing, is in addition to notifying the provider which goes through Oregon, we also directly notify families. So we send them letter of explanation. The card that you can see pictured here, which is real basic one-third of an 8 by 11 page, that we ask them to bring every time they see a medical professional. Whether it be in their rural village clinic or if they're needing to come into Anchorage for some

sort of care. Just to be sure that everybody knows and that this is a thing for this kiddo.

And then we also send them a DVD, which is also available on YouTube that was made a few years back by Matt and Dave and Thalia and some other folks. We send them this as sort of additional educational tool. We're hoping to update it and now with the event of DNA screening. But in the meantime, this is what we send to everybody with the hope that they are able to view it and get some more information in a different format. So then perhaps we ... Just then the letter and what have you. So we found that families that both watch the DVD and speak to a knowledgeable provider, have the best understanding of the disorder and on what they should do with their kiddos. We do spend a lot of time making sure they understand that their kids are normal unless ... That they don't need to do anything different unless they're ill. Which Dr. Hirschfeld is going to talk about here in a minute. Next slide please.

So, on that note. Dr. Hirschfeld.

Dr. Hirschfeld: Hey, this is Matt Hirschfeld. I'm up here in Alaska with [inaudible 00:31:33]. So thanks for advancing the [inaudible 00:31:35]. So essentially I work at Alaska Native Medical Center and we deal with a lot of the native people, pretty much exclusively. And so we see most of the kids eventually who have CPT1 arctic variant at some point. We also set a lot of policy for the regional medical centers, which are the rural parts of Alaska, around CPT1 and how they should treat it. So, these recommendations are something that we've developed over the last ten years in conjunction with Dave and Thalia and everybody else.

Essentially what we see is for kids who are healthy babies, healthy older kids, healthy adults, we basically don't see too many problems with hypoglycemia. If the kids are healthy, if they don't have RSV or flu, if they're able to eat normally and not fasting, those kids do really well. We do have, Dave had mentioned, a couple of studies earlier. One of the studies, we flew a bunch of kids down to Oregon Health Sciences for some fasting studies, and when we were talking to their parents about whether they ever have symptoms of hypoglycemia ... Some of the dads who were whale hunters or seal hunters, would describe getting really shaky, feeling sleepy, if they went for long periods of time doing lots of excess work in the arctic trying to stay warm and hunting. They would have to bring Snickers bars and some other candy bars to try and prevent those shaky feelings and the lethargic feelings from happening. They never got tested for low sugars, but that certainly could be symptoms of low sugars.

So it seems like we're starting to see people could have these symptoms, but we really don't see problems. Babies don't get into trouble, they don't have seizures, and they don't have any problems as long as they're healthy. We have some initial data that shows no increase and unexplained [inaudible 00:33:24] related events in kids who have CPT1 arctic variant. So, really it seems like healthy kids do best.

What we talk to parents about is if your kid is sick and has RSV or flu, respiratory distress, diarrhea, vomiting, anything that stops them from eating on a regular basis, those are kids you kind of need to watch. When we first messaged that, parents took home the message that they needed to feed their baby every day, all the time. Basically 24/7. And we had some really bad babies come out of Alaska Native areas in Alaska. We fine-tuned that message a little bit. Now people just feed their babies like they regularly would. If you're a newborn every two to four hours with breast milk or bottle. They don't have to feed their babies more, they don't have to feed them all the time. Just regular. We can start solids at a normal age, so somewhere between four and six months babies can start taking solids. Next slide.

However if your baby is sick, we want to look ... Have them look for the same symptoms that would make them concerned about any baby anywhere in the country. So, babies that are lethargic. Babies who are jittery or shaky. Babies who are crying and inconsolable. Who are breathing hard or fast. Obviously a baby who is not able to eat because they're so sleepy we can't wake them up to feed. Or needless to say, if a baby is having a seizure. Those are things that you should take your baby in right away to have them be seen by a provider.

And those symptoms aren't different from any other baby. They just may happen a little bit quicker in kids who have CPT1 arctic variant, who are also sick at the same time. So, babies should be seen ... Should be taken to their provider. At their provider's there should be a low threshold for starting a peripheral IV and getting some glucose-containing fluids in those kids. Next slide.

What we tell parents is if ... Especially if their babies are sick, they shouldn't go more than six to eight hours without being able to take some kind of sugar-containing fluid. So breast milk, formula, or Pedialyte. One of those. We also ... They can also try juice. We try and keep them away from Coca Cola products, just because that's kind of good practice. But if that's all they have, I've told health aides to give babies a little bit of Coca cola if they got weathered out. Just because there's some sugar in there. We don't use that as a normal thing. What's that?

Oh yeah, health aides are people that take care of patients out in the village.

Let's see. This is especially important in kids under two years of age, because that's where we seem to have the biggest problems with kids. And then where we also counsel parents is kids who are having surgery. So, when we first started diagnosing CPT1 stuff in kids in Alaska at Alaskan Native Medical Center, the first two kids we saw problems with were kids who came in for surgery who were made MPO for a long period of time and then kept having their surgery delayed. Then were run on IV fluids that didn't have any glucose in them.

So, we tell parents that when they bring a kid in ... When they know they have CPT1, tell the anesthesiologist and the surgeon that they have CPT1 arctic variant and that puts them in a little bit of a different risk category. They won't make them MPO as long, they won't delay their surgery and not start an IV with glucose-containing fluids. It's just something we've learned to do here in Alaska Native Medical Center. And if you are a kid under the age of two, who has CPT1, we'll put you first case of the day so that you're made MPO for the least amount of time and there's the least chance of getting delayed.

We also have a kind of strict MPO strategy. Instead of making kids MPO at midnight, or 9 PM the night before. It's six hours for solids and formula. It's four hours for breast milk and two hours for clears. So kids can have juice up until two hours before their surgery and we're very strict about that and allow kids to have juice or Pedialyte or something up to two hours before surgery just to keep their glucose up.

Also, when we talk about IV fluids, we're not running IV fluids at higher glucose or at a higher rate. It's just maintenance rate of [inaudible 00:37:29] glucose with some sort of salt in it. What that does, that allows you to keep your sugars up. We haven't seen that these kids need two times the maintenance rate or extra glucose. They seem to do just fine with regular maintenance glucose. Next slide.

So, let's see. [inaudible 00:37:50]. Okay. So, this is if you suspect arctic variant. Notify your last newborn screening. There are pockets of cases outside of Alaska and outside the Arctic. Like Dave was talking about before, we'll see Vancouver. We've seen some cases in Vancouver Island B.C. also Warm Springs Oregon. There's some interesting stories about the people from the Warm Springs Reservation in Oregon coming up and doing fishing experiences up here in Alaska. Maybe there's a connection there.

We treat ... So for symptomatic Alaskan Native kids, we treat for hypoglycemia as needed. Meaning we treat them with IV glucose. We diagnose and treat their underlying illness, which is usually in our case a respiratory illness. Because that's the most common thing we see up here. So if you get them through the respiratory illness, they really don't have any problems with CPT1. Next slide.

So that's kind of all we have. Just one more thing on health aides. I mentioned health aides earlier in the talk. Health aides are people who are ... Usually they're Alaskan Native people that are found in the village. They are high school educated people and they're the front lines of our health system in Alaska. Health Aides are ... They get a bunch of training here in Alaskan Native Medical Center on how to treat everything from a runny nose to a gunshot wound. They are amazing people. They have this giant book that basically if you show up in their office with a fever, you flip to page 860 in your book and it teaches you what to do with an adult with a fever. Or a two year old with a fever. All those kinds of things. So they're the front lines of our healthcare system.

And in the villages, as Sabra's and Jessie's map showed earlier in the talk, some of these villages, 100% of the people have CPT1 including the health aides and including the health aides kids. So the health aides are really versed on what the CPT1 stuff is, they really know what they're talking about and they're really the front lines on how to take care of kids with CPT1. So we've spent a lot of time talking to them about this over the years and if you're in a village and you have any kind of illness, they're the first provider you see. So after that, you get transferred to a bigger regional hub which has family medicine doctors, for the most part, in it. And if you're still sick enough that you can't be taken care of in the regional hub, that's [inaudible 00:40:13], you get transferred to us at Alaskan Native Medical Center.

Sabra: Yeah, we just had a case where this was the situation where we were thankful the health aide ... The mom brought the kid in. The kid was kind of lethargic. Kind of sick. The health aid knew the kiddo was CPT1A and took it much more seriously than perhaps with another kiddo than you would have. Or even if you're talking outside of Alaska. If mom says, well she's not eating well and she's pretty fussy. The doc or whomever is going to say call me in the morning and let me know how they're doing and here that's not what we're saying.

So we're addressing it immediately and if the kid needs to be transported or whatever, getting that started because we also have challenges here in just getting from point A to point B. That can take a significant amount of time. We don't have roads between ... When we're talking about going from the village to the hub, there's not roads most commonly. So it's we got to get them on a plane and of course if there's weather, which there often is, there are no planes. So we do have a lot of challenges with that. So it's another reason that it's important that we be proactive about any of these kids being sick. Or any of our kids with [inaudible 00:41:36] disorders, that we really don't want it faster.

So if you have any questions or want anything or want the link to the YouTube video that we have to watch it, please contact me. I can be kind of the conduit if you have questions that are appropriate for the lab or for Dr. Koeller or Dr. Hirschfeld. I can be the sort of main point of contact just for ease of streamlining. We would love to ... We love talking about this and informing people. Especially if you are seeing elevated ratios anywhere with a native population like we identified in Warm Springs. We would love to hear about that, to see potentially if it's another pocket that has shown up.

So, thanks.

Thalia: Thank you. Thank all of you. This has been great to hear what's been going on now that you've started DNA testing in Alaska. If anybody has a question, you can just *7 and unmute your line. Or you can type one in the chat box. For any of the presenters, including Marie from Connecticut on her profile of the state and the implementation of XALD screening there.

Debbie: Hi, this is Debbie [inaudible 00:42:58] and I had a question for Dr. Koeller. So, was there anything different about the kids that were identified by MSMS? Was there an increased sibling mortality? Was there anything that was different about why those kids' levels were higher in ratios? Were higher that they were detected by MSMS versus the other babies who were not detected by MSMS and carried the arctic variant?

Dave Koeller: As far as we know, there's nothing that seems to be associated with what the ratios happens to be. In other words, it's not as if the kids have seen that the ones with the highest ratios are more symptomatic or are more likely to have symptoms or anything else. I think a lot of it is similar to what we see with screening with the other fatty acid oxidation disorders, it depends a lot on the physiologic state when the sample was collected. I think in this case, since we're looking at that ratio, there's going to be other factors such as what was mom's carnitine level, because that would impact what the kid's total. In thus, the free carnitine level. So the short answer is, we don't have any real good information or why some kids were being picked up and others weren't. But as far as we know, they don't seem to be any sicker than the other kids.

Debbie: Thank you.

Carol Johnson: Hi, this is Carol Johnson from Iowa. I had a question or comment for Dr. Hirschfeld. So with our fatty acid oxidation patients in Iowa, we have an emergency protocol that we give the parents. We have a letter we give the parents. We have it if they're going to be seen in a university hospital, it's also in the online medical record. But they still ignore it, often, in the ER setting. I was wondering, did you guys do massive education of your physicians to get them to pay attention to fasting issues and the IV with glucose issues? Or any advice that you have to give those of us in other states who deal with this problem.

Dr. Hirschfeld: Hi, this is Matt. We did ... We have and it's ongoing. As Sabra said, I think earlier in her talk, we have a lot of turnover especially in the rural parts of the state. So we get a lot of locums and people who have obviously never heard of this before because why would you if you haven't lived in Alaska? So, we have ongoing educational stuff happening all of the time. We talk to ... We have meetings here at [inaudible 00:46:00] Medical Center, where we give presentations on this on a pretty regular basis. We try ... I go out to all ... Most of the rural places and every time I go out there, we talk about CPT1 and we talk about what the new stuff is with this. It's a lot of work to present all of this. Dave's been up here multiple times giving presentations. So we really do try and get the word out as much as possible.

It's changed a little bit since July 1st when we started picking up 750 of these babies a year up here in Alaska. All the sudden, now instead of me pushing the information out, I'm getting more calls from rural parts of the state that are asking me what's this CPT1 stuff? Which made me feel a little bit bad about my previous educational efforts, since some people haven't heard of it. But now

that this has become much more prevalent, we're seeing many more kids with this, not only are we starting to push information out but we're getting asked by different providers what's this all about?

For instance, our orthopedics department at Alaska Native Medical Center, has never heard of CPT1. Despite the fact that I've talked to them a couple of times about it. But they actually asked me to come by and give a talk to them. So even the surgeons, even orthopedic guys who care very little about metabolic disorders, are asking me about this because they're starting to see more kids who have this diagnosis. They just want to know more about it. It's ongoing. It's a big ... So far the biggest intervention we've had around CPT1 is education of providers, parents, health aides, everybody that we can find.

Sabra: And Carol, there's sort of a two-fold education process as well. In the one, knowing what it is and knowing what we want you to do. The other being don't overdo it. So we do occasionally get the ... For instance, we had a kiddo who was adopted to relatives out in California and the doc there panicked because they were only familiar with full on CPT1A and they sent this kid home with a glucometer. So we had to have them sort of step back. One of the other things we've learned, is just in how we communicate ... How we have our providers communicate to our families. When we use the word sugar, we mean a different thing than what families may hear. We say sugar, we mean formula, breast milk, whatever. And families hear table sugar because they don't know what that is. It's a two-fold education piece in both directions.

Dr. Hirschfeld: Occasionally we do mean table sugar if we can't find anything else.

Sabra: Right.

Carol Johnson: Exactly.

Sabra: Yeah, table sugar and the gums will do the trick if needed. Not as a first line ... We were having some families add sugar to bottles and things.

Dr. Hirschfeld: Carol it's also interesting up here, we have about 5 to 10% of our population in Alaska or Alaska Native, can't metabolize sucrose. So, that's kind of a pain in the neck when you've got CPT1 and you can't metabolize sucrose.

Carol Johnson: Wow, that's very interesting.

Dr. Hirschfeld: That's why we go after the formula or breast milk because that's lactose not sucrose.

Carol Johnson: Right.

Sabra: That's next on our list of things to tackle.

Carol Johnson: I wouldn't feel bad about your education efforts prior to the phone calls you're getting because I think it's the phenomenon of leading a horse to water, right? They don't know that they need to know until they need to know it, right? So, don't feel bad that people were ignoring you. And thank you for your answers, both of you. That was very helpful. Thank you.

Sabra: Thanks Carol.

Cindy: Carol, this is Cindy in Vermont. And just to follow-up on your question, for certain disorders, primarily the fatty acid disorders, our metabolician here in the state has added a message that pops up. So when the physicians, especially in the emergency department, open the babies' electronic record, in great big bold letters it says, this baby has whatever. [inaudible 00:50:19]. The parents are very familiar with it. Listen to them. Exclamation. Exclamation. And I think that does attract some attention because it's the first thing they see.

Carol Johnson: And I agree. I think that's a great strategy and it works in some places and just not in others. If they don't have an electronic medical record or ... God bless sticky notes, right? Because sometimes there's a sticky note inside of the old fashioned paper chart, and that's how people know about it. But even when we've had parents wave this in front of people's faces and talk about it, they've still been ignored. Which is frustrating to the parent and frustrating to us as well. So ...

Dr. Hirschfeld: We're actually talking about doing that at Alaska Native, too. In about three to five years, the entire tribal health system up here will be on [inaudible 00:51:17]. If you ... No matter where you are, you'll have the same medical record and everybody in tribal health will be able to see your complete electronic medical record. So we're talking about the CPT1 ... The people that have been diagnosed CPT1 as little flag on our EHR and we're just trying to figure out how to do that where ... When half of your population that has it.

Carol Johnson: Right.

Dr. Hirschfeld: Great idea.

Carol Johnson: Very cool that you ... That they're all going to be on the same system too. That's great.

Sabra: One of the things that we learned, we did a little QI project with some of the families. I think I mentioned that if we know that if they watch the DVD and they talk to a knowledgeable provider, that they sort of have the best knowledge and understanding. But the one thing that was a little bit, maybe ... I guess not surprising, but that we weren't expecting, was that if they hadn't watched the DVD and they talked to a provider who was not knowledgeable, it wasn't even that they were less knowledgeable about the disorder, they were scared. So they were ... People who never talked to anybody and didn't watch the DVD,

just had no knowledge. But people who had talked to a provider that perhaps gave them less than ideal information, and that was pretty clear. They'd say what the provider told them and it's pretty obvious that that was basically direct quotes. So that was an eye-opener that we really need to make sure that our providers are clear with families and aren't making them more fearful than they might be at baseline.

Carol Johnson: Thank you. Does anybody else have any questions?

Thalia: I don't have any in the chat box either Carol.

Carol Johnson: Okay.

Thalia: But I wanted to say something before we do sign off today. I'm going to put this title side up. Just let those on the call know, if you have suggestions for future calls, we always ask for your feedback. The new contact for this is Sikha Singh since I will be retiring next week. So contact Sikha, if you have any suggestions for the future webinars, topics. The work group is always welcoming topics so they know what you're interested in hearing.

Sabra: I think I can speak for everybody in Alaska and Oregon, in wishing Thalia well in her retirement and thanking her for everything she did around CPT1A and just in general for newborn screening up here. And has continued to be supportive and we wish her well and good luck and we'll probably still be bugging you.

Thalia: Thank you so much, I appreciate it.

Cindy: The same from the Northeast Thalia, we're really going to miss you.

Thalia: Thank you.

Carol Johnson: Thank you to our speakers, all were excellent presentations today. Thank you. And a big huge thank you to Thalia for all she's done for short term follow-up group.

Thalia: Thank you. Thank you for attending this month and the next one will be on May 8th so look for announcements through the listserv.

Carol Johnson: Thank you everybody. See you in two months.