NCHAM
Webinar Series: Universal Screening/The Ontario Story
Friday, September 4, 2020
11:30 A.M. ET
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>> ALYSON WARD: Good morning, you should be hearing audio now. If you are not receiving a strong audio signal, please adjust the volume settings on your computer or your headset. If you still do not have audio you may need to sign off Adobe Connect and come back in and hopefully that will improve your connection. If you have issues even after testing that, please contact Daniel at the number highlighted in red on your screen.
(Standing by).

>> ALYSON WARD: Good morning, we will be starting the webinar "Universal Screening/The Ontario Story" in about five minutes.
(Standing by).

>> ALYSON WARD: You should be hearing audio now. If you're not receiving a strong audio signal you may need to adjust the volume settings on your computer or your headset. If you still do not have audio, you may need to sign off and come back on. And hopefully you'll get a stronger connection. In the meantime I'm just going to do a quick poll here to test the audio quality. Please mark on the poll your audio quality. It will give us a good sense of what people are hearing. Excellent, it looks like most are coming in with good to excellent audio. Again, if you need help with your audio, please contact Daniel in the number over here on the left-hand side of your screen.
(Standing by).

>> ALYSON WARD: We would also like to get a good idea of who is attending today's webinar. If you'll go ahead and mark what best represents you. That would be

excellent.
(Standing by).

>> ALYSON WARD: I'm having some challenges here expanding the screen. Mandy, can you see if you can expand the box?
(Standing by).

>> ALYSON WARD: Interesting. The box isn't working as it's supposed to. So sorry about that. Okay. We will be getting started in just about one minute.
(Standing by).

>> ALYSON WARD: Okay my apologies the Adobe Connect on my end is having an issue. Please stand by.
(Standing by).

>> ALYSON WARD: In the meantime please take a minute and just indicate what best represents you and your reason for joining today.
(Standing by).

>> ALYSON WARD: Okay welcome to the last in the Webinar Series of CMV Research and Innovations webinars. We're really excited to welcome Pranesh Chakraborty today as our presenter. Before we turn the time over to him, we're going to start with a parent story. And first of all, I'm going to go ahead and press record. And I apologize, there always seems to be a little bit of something that happens every day that makes this -- keeps this exciting and keeps me on my toes. I'm going to go ahead and start recording.

>> OPERATOR: Audio recording for this meeting has begun.

>> ALYSON WARD: Excellent so my name is Alyson Ward. I work at the National Center for Hearing Assessment and Management. We're located at Utah State University up in northern Utah. We are the technical Resource Center for all the U.S., states and territories for their Early Hearing Detection and Intervention Programs. And as such that really drew us into the link between hearing loss in infants and young children due to congenital cytomegalovirus. We started the CMV Public Health & Policy Conference back in 2014 and right now we would have been in Ontario and unfortunately, that is not happening due to COVID-19 which has just changed the trajectory of all of our lives. But we really do appreciate the opportunity to hold these webinars this week.

So NCHAM as well as CMV Canada and the National CMV Foundation are sponsoring this week's webinars. And please save the date for our in-person meeting which will be in Ottawa Ontario next August, so August 22nd through 24th. So please save the date. And plan to join us there.

And as such in all of our past conferences, as well as the webinars this week, we've really wanted to highlight parent stories.

And as you can imagine, you know, we've really got to keep parents at the center of this conversation and they have been an excellent catalyst for change over -- you know, over the last six years plus with the CMV initiatives across the U.S. and in Canada and

beyond. So we're going to hear from William Jones. We're going to share both a parent story that he has videoed. And then the Ontario team sent me an amazing kind of news clip that also highlights the role that the Jones family played in the Ontario screening. And being identified.

So let's go ahead and hear from William first. And hope that Adobe Connect wants to play nicely okay let's go ahead.

>> WILLIAM JONES: Hi my name is Will I'm the father of Francesca Jones. We knew something was going on when the fire alarm went off and she didn't stir we thought it was weird she didn't move the next morning it was confirmed there was something up because she didn't pass that first filter of the hearing test for newborns. And so we were referred for a follow-up test two weeks later and it was there, it was a more invasive test and we found out yes there's a serious issue with her hearing. And at the time there was this -- do you want to opt in for this new program to test the blood spot against this one virus called congenital cytomegalovirus. So we thought, why not, you know, let's get her tested and see what's going on.

Little did we know a few days later that she tested positive and she was the first caught through this program in Ontario. And excuse me. She -- we had a whole team of people, great people, who infectious disease specialists, physiotherapists, audiology team. Auditory language therapists. We had this whole great team who just really helped us along the path. She was outfitted with hearing aids to see if that would even just get sound until she could get her cochlear implants. And at one point at five months down the road it came up that she could get bilateral cochlear implants. She was implanted then six months later in that same calendar year, December 2018, she is six months old and her sound was turned on and since then, you know, I'll never forget doing all of these different exercises, all of these appointments that we have done. And all this great team we had to get her to this point where we're shaking rice in a tupperware to see if she could localize the sound and now I'm picking her up at day care she's two years and three months old I ask her are you ready to go home and she says no we have to wait for Pramika to go get my sweater first papa. I'm blown away with her language development and I'm blown away with organizations like CMV Canada and SickKids and all of these organizations that really have just helped us care for our daughter. And I'm so thankful for everyone in this room. To just be providing this great care for all of these kids that deserve it. And I'm just so thankful and thank you so much.

>> ALYSON WARD: Thank you for sharing your story, William I don't know about you all but I definitely get goosebumps every time I hear parents' stories. They are always very unique to that particular family. And it's really exciting to see when things work well like they did for Francesca.

So let's take a look at this little news clip. And this is Francesca getting her cochlear implants turned on for the first time. And enjoy it. It's pretty exciting.

>> So what we're going to do today is program Francesca's processor so sound can

go in and she can begin to hear. So this is the day we have been waiting for. We want to give her some sound gradually. And we're going to have you guys over the next couple of days increase the levels so that they become a little bit louder. But today, even though she's going to be having sound in both ears, the sound is going to be really, really soft and we do that purposefully so she's not overwhelmed or too frightened to wear the processors.

(Beep).

>> So that was two -- she's happy.

>> Francesca.

>> Hi, Francesca.

>> To put sound on is unbelievable. It seemed like it was a race against time to get sound in as fast as we can. And I mean, we couldn't with the help of everyone, we couldn't have nipped this any quicker.

So Francesca failed the hearing test before we left Mount Sinai Hospital. And then two weeks later we went for a follow-up hearing test. At another clinic. And she also had failed that test, as well. I received a phone call from an Ottawa area code and I didn't know why is anyone from Ottawa calling me. And it was the center that had tested for CMV. And she tested positive.

>> So congenital CMV is the most common congenital infection. It happens in about 1 in 200 babies. Most babies with congenital CMV never have any problems, about 80% of them but about a fifth 20% will come onto develop some sequelae the most common which is hearing loss.

>> What's special about Francesca is the very first baby identified in Ontario through this new expanded screening program for CMV. The other special thing about her is she is the second youngest child that we have implanted here at the Hospital for Sick Children so the fact that we were able to get cochlear implants into Francesca by the time she was five months of age and her activated shortly after six months of age means that her developmental trajectory from a hearing standpoint will be no different than her normal hearing peers.

>> I want to thank the Kids and the entire team for giving us the best Christmas gift. This is the ultimate Christmas gift. Santa Claus was good to us this year. Yeah, that's -- just thank you. That's all I have.

>> ALYSON WARD: Yeah, very cool video indeed. So thank you again to the Jones family for sharing their story and then for sending on that news clip.

So I'm going to turn the time over to Dr. Pranesh Chakraborty. Since 2007 Dr. Chakraborty has been the medical and laboratory director for Newborn Screening Ontario and also sees patients with inherited metabolic disease at the Children's Hospital of eastern Ontario in Ottawa. Or CHEO the acronym is his undergraduate and post graduate education took him on a tour of the province of Ontario he completed his medical school at McMaster University in 1993 and specialized in medical biochemistry at western university pediatrics at the University of Ottawa and finally subspecialized in

biochemical genetics at the University of Toronto he joined CHEO in 2003 as a metabolic physician and co-authored the modern newborn screening program in 2005 and led its move to Ottawa in 2006. His research is on improving outcomes for patients with IMD, newborn screening and metabolics.

So I'm going to go ahead and turn the time over to Dr. Chakraborty.

>> PRANESH CHAKRABORTY: Thanks, Alyson. And also I just want to thank William and his family, Julia and Francesca for their sharing that story. Certainly it was very meaningful to us after many years of work to get to where we are right now.

I also want to thank the organizers for asking me to speak. It's my first time speaking in this kind of format. So we'll see how it goes. So far so good. I'm usually someone who feeds off of looking at people in the audience. So I'm usually not used to staring at my slides. I also want to call out and thank Robert Tetro at CMV Canada for all of his advocacy for over many years. And so just want to say thank you to him, as well.

So let's see here.

So today I want to talk about the Ontario story. And what we're doing. And how we got to where we are.

And also to give a little bit of information as to where we are after the first year of the program.

Okay. So really, you know, there's one objective, how did we get here. And two time points, July 2018. We started hearing-targeted CMV screening using newborn dried blood spots. And in July 2019, we started on universal screening for cCMV. Right off the bat, you know, it will be the theme of this talk. You know, I would change that second point to Ontario starts universally offering testing dried blood spots for hearing loss risk factors. And that includes both cytomegalovirus DNA and genetic risk factors.

And I think this is particularly important in terms of understanding how we got to where we are. What it is exactly that we're doing. And it's an important distinction in terms of the policy process to get there.

And so hopefully by the end of the talk, you'll understand that nuance from the perspective of how we did things here.

Or have done things so far here. It's never a done thing.

So I wanted to start with the definition of what a screening -- of what is screening. And we had a Task Force to define screening in the context of newborn screening. In 2011. Or so.

And the -- you know, that was in response to a question we got from people at our Ministry of Health to define newborn screening a bit better. And they had things in mind like, you know, is newborn screening, does that mean that it has to be a disease that presents in the newborn period? Or does it mean that you're screening newborns for disease that could appear later? They wanted to be more precise as to their understanding from a policy perspective.

So here is the definition we came up with in our Task Force. Was that screening is

a systematic population-based application of a test or inquiry to individuals who do not have symptoms of a specific disease or condition in order to identify those who warrant further investigation and/or intervention to achieve better outcomes.

So that's a pretty packed definition. But if I were to break that out a little bit, screening tests are about an asymptomatic or minimally symptomatic population. You know, people in a population who may not know that they have a condition or may not be recognized as having a condition. It's about risk estimation. Understanding whether they are at increased or decreased risk. And really that's for a particular outcome. That you want to optimize.

So screening is an activity aimed at bettering outcomes by starting treatment early in the course of a disease.

So where did the practice of newborn screening come from? And why did a metabolic physician like me get so deeply involved in screening over the years? And really the story of newborn screening is a story of an inherited metabolic disease, PKU, phenylketonuria would be the name of the disease there were several things that happened in the increasing understanding of PKU it led to being the first target of newborn screening. And in most jurisdictions, that screening started in the 1960s.

So the understanding of what PKU was was first delineated by a Norwegian physician, Folling in 1934. And it was the first recognized disease caused by genetic variation on -- impacting on the metabolism in people.

It was recognized as a very important cause of mental retardation. And you know the next important observation was that there was a treatment that could prevent the cognitive disabilities. So that question of, is there a treatment that could actually prevent the cognitive disability in patients with PKU was sorted out in the 1950s. Bickel is often credited with that but as with most things like this, there was a group that was involved.

Including a Canadian physician. So it was as usual an international effort. So PKU is a disease. There's a treatment that can prevent the major adverse outcome, which is severe cognitive disability in this disease.

And then the third major advance was answering the question of whether there's a reliable, simple and sensitive test.

And that was Bob Guthrie. And that's a picture of him on the slide there. In the early 1960s. Who developed really two technologies. One was the dried blood spot, which continues to be a very important technology. And I would argue is most important innovation. It was a way to take a small sample of blood on which you could do testing. And a way to take it that allowed you to stabilize the components of the blood and the things that you wanted to test for them in and also transport that blood quite easily to a centralized testing facility.

There have been previous attempts to screen for PKU using urine testing within family physician offices or primary care settings and the biggest issue there was quality assurance. There were very large numbers of false positives and false negatives. And

so this innovation of the dried blood spot was very important and he also invented a test to measure the phenyl which did help pick up kids who had PKU. We now knew that PKU was a disease. We knew severe mental retardation could be prevented by early dietary treatment. And there was a reliable, simple and sensitive test developed by Guthrie that could be applied to find those kids with PKU so that they could have their treatment.

And one thing I forgot to mention, which is vital, is that the treatment had to be instituted before the onset of any recognizable symptom in order to achieve the desired outcome.

So if a baby or if a toddler was already having some cognitive disability, that was not reversible by the District. And still now there is no known treatment that could reverse the cognitive disability in a patient with PKU.

Newborn screening, therefore, really started as a public health emergency. We saw the spread of newborn screening very rapidly in industrialized society. And you know the burden was estimated at roughly 2, 2 to 4% of severely cognitively disabled institutionalized people having PKU. And again this fundamental concept of the treatment before the onset of symptoms was transformative. And in this case, resulted in a normal IQ.

So in terms of screening, you know, I've talked about where newborn screening came from. This paper really a treatise from Wilson and Jungner published in 1968 by the World Health Organization I would argue continues to be one of the most important if not the most relevant paper describing principles of screening. And this is really not limited to newborn screening. But screening in general. Including screening for cancer or screening children for developmental disabilities, any type of screening.

And they really delineated ten important principles. And I will read them out. And I will come back to this in terms of how the policy consideration happened in Ontario.

So one is the condition sought should be an important public health problem. Just to note that these are verbatim from the text. These are directly quoted in the way they wrote them.

The slide I had previously, I had paraphrased or tried to shorten it to clarify. But I thought it was important to go back to the exact words.

So 2, there should be an accepted treatment for patients with recognized disease.

3, facilities for further diagnosis and treatment should be available.

4, there should be a recognizable latent or early symptomatic stage.

5 there should be a suitable test or examination. 6, the test should be acceptable to the population. 7, the natural history of the condition, including development from latent to declared disease should be adequately understood. 8 there should be an agreed policy on whom to treat as patients. 9, the cost of case-finding, including diagnosis and treatment of patients diagnosed should be economically balanced in relation to possible expenditure on medical care as a whole. And 10, case-finding should be a continuing process and not a once and for all project.

Now, for anyone who has not read the treatise, I would encourage you to read it. Especially if you have an interest in screening and especially newborn screening for CMV or for permanent hearing loss.

Through their treatise they use PKU as a bit of an exemplar of a disease that does demonstrate these principles very well and goes into a much more nuanced discussion as to what each of these mean.

I should say meant to them or how they can be importantly interpreted. So it is a read I would encourage you to pursue.

Now, one of the important things to note is that screening involves a system of care. It is systematic in how it is done. As part of our Task Force to define screening we also try to define the important parts of that system of care. And we broke it down into these headings of education, enrollment and consent. Those things all interact with each other. The screening test self and its interpretation. The process of retrieval, diagnosis and treatment. And I think in Francesca's story that William shared there, they talk a bit about that journey of having a baby. And a baby who is not recognized as having any health issues or issues that might need some intervention. And then that baby is retrieved. So that's what the term retrieval means is you have someone who is not a patient. Who is brought into a system of care. And they have to be brought back.

And then they go through a journey of diagnosis and eventually interventions and treatments. Other parts of the system include data management and performance measurement. And obviously an overarching concept of policy setting and governance.

So I want to say a few words about Newborn Screening Ontario, that's where I work. And it's a provincial program based at CHEO academic Children's Hospital here in Ottawa at NSO we're responsible for the dried blood spot and critical congenital heart disease screening to all babies born in Ontario and since we were established in 2006 in our hands we have screened over 2 million babies. And about 2700 or so babies have been diagnosed and treated early with 1 of about 25 target diseases of newborn screening.

Newborn screening in Ontario for PKU started in the mid 1960s. And was handled at the public health branch prior to coming to Newborn Screening Ontario at CHEO. And part of the reason for the move was with the expansion of newborn screening and increasingly rapid expansions in newborn screening, ties to research, ties to the academic healthcare system was felt to be important. And there was a desire at the time to move the testing and coordination from the public health branch into an academic pediatric Health Center.

I must say this is something that's a little bit different in Canada than in the United States. And where screening remains largely an activity of state public health departments.

But in Canada, it's relatively common to have the newborn screening programs coordinated out of each province's academic pediatric hospitals.

The cartoon here does -- illustrates our overall structure. You know, some of those

core concepts of a system of care are captured in here.

You know, babies in Ontario are generally born either in hospital at certain birthing hospitals or they can be born at home or community birthing centers under midwifery care. As a whole as a group we call those places and those people the submitters. They are typically submitting a dried blood spot sample. Those are shipped from across the province to our lab in Ottawa. And we perform the testing. And refer babies -- and these are medical referrals that we make to the children's -- generally children's hospitals. Where they have treatment centers who perform the retrieval of diagnosis and initial treatment and ongoing care for babies identified. By screenings.

We have an Advisory Committee. And we report and have accountability to the Ministry of Health.

Ontario also has an Infant Hearing Program and this really is Ontario's EHDI program. And it has responsibility for a Newborn Hearing Screening. So the Ontario Infant Hearing Program is a comprehensive program to identify infants with permanent hearing loss or at risk for late onset of progressive PHL or permanent hearing loss and provide them with the supports and services required for communication and language development so they are as ready to learn as possible when they reach school.

Again, the IHP, so the Infant Hearing Program, provides Universal Newborn Hearing Screening, audiology assessment, hearing aid selection, follow-up audiology -- follow-up audiology visits, family support services and communication/language development services for children until school entry.

So again, what I'm describing is they provide the comprehensive Early Hearing Detection and Intervention Program in our province. As with any places the program the targets are screening of newborns by one month of age and identify those born deaf or hard of hearing by three months of age and starting intervention by six months of age.

This is all predicated on the observation -- while I won't go into the evidence in this talk, but you know I would say strong evidence that children who meet these targets will develop language comparable to their hearing peers by the time they enter school and this is very important both from a language and communication development perspective but also from a global development perspective including cognitive and social aspects of development.

The program is delivered through 12 regional lead agencies across the province who are responsible for delivering the program in accordance with the provincial guidelines and in a manner which reflects the regional and local needs.

So I think I've already covered this. So I won't go into detail. But you know the Universal Newborn Hearing Screening system is an important program component. But I do want to highlight here the surveillance screening is also an important component and provided for all infants born at risk of developing hearing loss in early childhood so the IHP Infant Hearing Program, in Ontario has an existing -- had an existing stream for surveillance screening and for identifying infants born at risk of developing hearing loss

in early childhood. And this is important in terms of the context in which we were looking at CMV and genetic risk factor screening.

Okay. This slide just provides a bit of a timeline to illustrate the changes that have occurred in Ontario this is not dissimilar to the types of changes that I think have been seen throughout North America in newborn screening. As I've mentioned at the beginning, screening for PKU -- oh, there it is. I have this little pointer here. Screening for PKU started in 1965 and in many places it did start in those early to mid '60s. For many years nothing was added, nothing was changed in terms of a target panel for screening. In 1978, congenital hypothyroidism was started. And that was really an innovation out of the province of Quebec in Ontario where a lot of the work to prove that screening for congenital hypothyroidism was another important way to prevent cognitive disabilities and growth problems in the children who were affected.

And again, there was a fairly long gap. You know, I haven't -- this timeline doesn't show things to scale. But from 1978 to 2002, there was very little change. And there was increasing unrest I would say in the child health community as there was an increasing number of conditions, including Sickle cell disease, including MCAT deficiency and our metabolism and in Ontario there was a bit of a policystasis at that time and some of the American jurisdictions and Canadian jurisdictions acted before Ontario in terms of the dried blood spot system. But Ontario was a leader and was at the forefront of implementation of Universal Newborn Hearing Screening. And establishment of an EHDI program. Both internationally and within Canada. And in 2000 to 2002, there was an implementation of UNHS, so Universal Newborn Hearing Screening in Ontario as part of the Infant Hearing Program.

In 2006, that's when NSO was established at CHEO then you can see a very relatively rapid expansion including many additional dried blood spot screening targeted diseases were added in that time.

So the political climate at the time, the health minister at the time would often say we want to move Ontario from worst to first and I guess it's one of the pluses of having fallen behind your peers. Often there can be a policy driver to want to at least keep up with, if not lead your peers in appropriate change. In 2013, screening for severe combined immune deficiencies were added so those are sometimes referred to as quote Bubble Boy diseases where babies are born without a functional immune system in 2017 we took on responsibility for coordinating the pulse oximetry based clinical congenital heart disease screening in Ontario where the oxygen saturation of babies is measured as a risk indicator for whether they might have a critical congenital heart disease and this was our first foray into screening at Newborn Screening Ontario into screens that were involving a test being done at point of care.

And what I'm going to describe today was in 2018, we moved to the first phase of what we called the hearing risk factor screening. And that involved the hearing targeted testing of dried blood spots for CMV DNA. And in 2019, so just over a year ago, we started in Phase 2, which was the universal offer of CMV DNA. And testing for some

genetic risk factors using dried blood spots.

And change doesn't stop. Just a month ago we launched our screening for spinal muscular atrophy and Hurler disease. And just to note that Hurler disease is quite rare. But babies with Hurler disease almost invariably have ear, nose throat problems. Including both the possibility of conductive and sensorineural hearing loss. So not directly related to our talk but very related still to hearing screening and early hearing loss detection.

So this is a slide I won't dwell on other than to say that I have three kids. And very carefully followed their screening experience. These are pictures of my first child born in 2011 having her blood spot screening. This is her having her otoacoustic emissions screening. My youngest child, was born just before we started the congenital heart disease screening. And we kind of beta tested her at home. This is her having her pulse oximetry done about a month before we formally launched the program. And of course, none of them has a target disease. But just to illustrate what we're interested in is optimizing outcomes for all children and letting them reach their potential. And also an illustration that we're often talking about diseases or conditions which may be at high risk within a family. So whether they are genetic or sometimes infectious diseases. But the there's the child but also the child's family that is important to consider.

Okay. So when we looked at the Universal Newborn Hearing Screening program, when I say we, I was going to get to this a bit later but I think it's important for context to note that starting in around 2009, 2010, Stacy Weber and I Stacy is at the Ministry of Children -- it was the Ministry of Children and youth services at the time and was responsible for the Infant Hearing Program. We started talking about how we could work together to improve newborn screening overall in Ontario.

And so this is a conversation that's been going on for a long time. So overtime, we -- after many discussions we identified some challenges with Universal Newborn Hearing Screening that we were interested to see if we could do something about. And some of these challenges included identification of infants at risk for non-congenital hearing loss. And what could we do to improve that? Recognizing that risk assessment is difficult. Often involve a chart abstraction, it's also fairly insensitive. There's also a lack of specificity in trying to understand some of these risk indicators. And also what needed to be done to improve surveillance.

And so both in terms of who should be surveyed. And that's where better assessment of risk indicators might be important. But how often. And until when should they be surveyed and the Infant Hearing Program has been doing a lot of work Marlene Begatto at western university has been doing a lot of work and many others over time in terms of improving the surveillance protocols.

Second, identification of infants with congenital hearing loss who pass the audio metric screen. And I would add here, also, is there anything that could be done to identify infants who didn't get an audio metric screen so both finding false negatives for babies with congenital hearing loss. Then the etiology of hearing loss is often unknown,

uncertain or presumed on the basis of risk indicators. And when might there be a need for additional or recurring audiological assessments. And Martin Hyde was a prominent figure in infant hearing in Ontario for many years. Often would bring the question of auditory neuropathy in this context if you don't know etiology if you don't know who you potentially missed in screen, you know, how can you best tailor their audiological assessments. And then also prognostic information in terms of treatment decisions and is there other medical follow-up if needed? Is this only a hearing problem? Or are there other potential medical issues that might need follow-up?

So from the inborn air metabolism world where I clinically live, most of the physicians there are aware of babies with Hurler disease which I mentioned we just started screening for in Ontario. Who have been diagnosed through a hearing screening pathway. And were having augmentation that hadn't had medical follow-up to diagnose their Hurler disease.

But these were all issues. And we started talking about what could we do or not do to try to improve those things?

So this is a paper and a concept that I think everyone on this call is likely aware of. So Morton and Nance in their New England Journal paper in 2006 pointed out many things but including what is the incidence of permanent hearing loss at birth. And then what's the prevalence of that permanent hearing loss later in life? And recognizing that you can have early permanent hearing loss, which is non-congenital.

And so what could we do to identify those children at risk?

And what's the scale of this, you know, it's about a doubling. Of children if you take all kids who have permanent hearing loss around the time of school entry, just over half of them will be congenitally deaf. And you know, the others will develop their hearing loss over time.

So if you look at the etiology of that permanent hearing loss, the two big players here are genetics. With GJB 2 and SLC 2684 being the big hitters on the genetics side and congenital cytomegalovirus infection being the big hitter on the environmental side.

So they pointed out that if you could screen for these three causes, and what they meant here were some genetic causes, including the two that I mentioned, they include a third one, which we don't screen for in Ontario. So screening for these three causes of late onset hearing loss is performed together with the presence for the test of CMV we recognize the follow-up of at-risk infants should result in detection of nearly 60% infants in which late onset prelingual hearing loss develops as well as immediate etiologic diagnosis for at least 40% of those with congenital hearing loss.

Okay. So that's a long preamble to say what was the policy process in Ontario? Was it should we screen for congenital CMV infection? Or should we enhance screening for early permanent hearing loss risk? And I think from everything I've said today, it's clear that the what the policy process was and the questions that were being asked in Ontario was really -- they were really around the second question, should we enhance screening for early permanent hearing loss risk? The policy context was to

improve and enhance the Infant Hearing Program primarily the UNHS, the Universal Newborn Hearing Screening component. And to bring together the two newborn screening programs, the IHP and NSO to achieve this.

And the expected enhancements were to move from a landscape where we had some challenges. Things had been working exceptionally well. But we always want to improve. And to try to address the challenges of some limitations in the detection of non-congenital permanent hearing loss. Some lack of focus on etiology. Cases not identified through screenings so false negatives. But also missed screens, trying to identify babies who may not have had their hearing screened.

One thing I didn't mention is that we knew that there were more babies having dried blood spot screens than having hearing screenings so bringing the two programs together was seen as a way to address that as well so moving to early detection of non-congenital hearing loss, and improve etiologic focus. Improved sensitivity of the overall UNHS program. And improving access, fewer missed screens.

>> ALYSON WARD: I'm just going to interrupt you for a second and let the attendees know that I opened up the question box on the left-hand side of your screen so go ahead and enter your questions there and we'll begin answering those questions in about four or five minutes.

>> PRANESH CHAKRABORTY: Sounds good. And I will accelerate through this slide.

So I wanted to come back to the Wilson and Jungner principles and to look at the question that we looked at the permanent hearing loss risk factor screening question. Versus you know some of the challenges that I think this audience may know in terms of the question of congenital CMV screening.

And you know, this may be relevant to processes like adding conditions to the rusk (phonetic) panel in the United States. And if you approach the question from the perspective of screening for cCMV, there are some subtle but important differences I think in how these can be conceived. And some of the issues and questions that come up. Including context.

So first principle is is it an important public health problem? And you know, really I've put some words in here. And you can read it. But I think there's no question in anyone's mind that both present an important public health problem. But they are different public health problems that overlap significantly.

The second, is there an accepted treatment for patients? And I'm going to jump over to the permanent hearing loss risk factor slide and I think for a long time there's been a recognition that early communication and language services, or hearing interventions, lead to improved cognitive and communication outcomes, regardless of etiology of the hearing loss.

And recognizing in a timely way all -- as many babies as possible and as many children as possible with that -- without permanent hearing loss is very important to achieving these outcomes. In terms of CMV screening, the question of treatment often

comes back to a question of treating with antivirals.

And certainly in the timeline in which we have been considering this in Ontario, it was before the valganciclovir came out in the New England Journal. And so often you'll hear some questions and concerns around the acceptability and the treatment using valganciclovir including the -- how big of an impact the valganciclovir can have and what are the potential risks of treating asymptomatic children or those with isolated sensorineural hearing loss what's the quality of evidence to date and I know Dr. Park spoke a bit about the Val Ear Trial which I think is an extremely important trial to be doing. How long to treat, et cetera.

So a lot of questions around treatment. And some of these questions are questions that our Advisory Committee brought up quite strongly, the ones that I'll bring up here if we had been considering congenital CMV screening in and of itself and not as part of permanent hearing loss risk factor screening, I'm not sure it would have happened in Ontario.

What are the facilities for diagnosis and treatment? And in either case, there needed to be a new medical care network to take care of and work up the kids who were identified with having congenital CMV. In terms of the surveillance and you know the ongoing audiological care, having it as part of an existing permanent hearing loss risk factor system was definitely extremely important and helpful.

Is there a recognizable latent or early symptomatic stage? And you know in terms of screening for permanent hearing loss risk factor, I think Dr. Park talked a bit about this yesterday, but the hearing loss risk in babies with congenital CMV is quite well understood. I think there are some open questions still about the long-term natural history of babies, especially with asymptomatic CMV. And being able to predict some of those potential adverse health outcomes, especially in those children with asymptomatic CMV.

So just going through the remaining criteria, is there a suitable test or examination? I think this is also a very important one. I know in the considerations for the rusk in Ontario or in the United States, there are a lot of concerns about the sensitivity of the DBS testing and I think it remains an open question as to what the sensitivity is but it's almost certainly not going to be 100% sensitive. But if we looked at it from the permanent hearing loss risk factor perspective where there's already an attempt to identify children with congenital CMV as an important risk factor, this was seen as a change that would improve the overall sensitivity of this important risk factor for hearing screen. So apparently major difference in the approach and interpretation of the same data on sensitivity of blood spot testing.

There have also been questions about test acceptability in the population and those same concerns exist within the permanent hearing loss risk factor context. But being offered in that context also in Ontario allowed the opportunity to consent for testing at the time that hearing screening was offered. The hearing screen in Ontario occurs in a consented manner.

As I'll remention some of the questions around natural history of especially asymptomatic CCMV and to note there's often a core predictor of what the risks are for later onset. I'm not sure if Scott Gross is on the call but I think he would say the cost effectiveness is unproven I think the paper was very helpful in suggesting it might prove very well to be cost effective but both approaches would need to be evaluated after some time.

And in both cases, case finding was intended and will be intended I think to be a continuing process.

So the policy process at Ontario I think I've described that here. It was led by the child services with support from the Ministry of Health. And the screening principles primarily considered from the perspective of the Infant Hearing Program with risk of permanent hearing loss by age 5 as the official target of screening.

So cCMV was not the target of the screening. It was a risk factor for that target.

The decision was made to augment the Infant Hearing Program led hearing screening program with secondary testing of the newborn screening blood spot for CMV and for certain genetic mutations.

Enrollment and consent was part of the hearing system and not the dried blood spot system and there needed to be data sharing between the programs, education and training would need to be shared. And there would need to be new systems for referral of screening positive infants with both a medical referral system -- I forgot I'm not pointing but both a medical referral system and care system as well as an audiological care and surveillance system.

The latter would be fully integrated within the existing systems in the Infant Hearing Program.

>> ALYSON WARD: So Pranesh I just want to check in with you. We have about seven minutes left in the webinar time.

>> PRANESH CHAKRABORTY: Yes.

>> ALYSON WARD: And we have several questions that have rolled in. There's clearly a lot of information to cover in the process that Ontario has gone through to get the universal screening system in place both in the dried blood spot queue as well as the practicality of actually implementing it in the hospital. I'm just curious, you know, I would like to move to questions now. And if -- and we can connect later and see if we need to do like an Ontario story Part 2. Because there's still a lot of information that I know you would like to cover. And I think that the attendees today would like to hear more about some of the application and getting the screening program up and going.

Are you okay with that approach?

>> PRANESH CHAKRABORTY: Yeah, and I've been looking at some of the questions on the side as I go. I think I just -- I think it would be helpful to just run through the last two slides so I've skipped over the intervening ones. Because some of the questions have to do with what we have observed to date so the slide that's here now showed the experience with Phase 1 which was the hearing targeted. In that time

period, there were 2,000 babies screened and these were the babies who needed to go to further audiological assessment. 96 of them were consented. We have 17 DBS screened positive for CMV and here you can see their outcomes. In terms of hearing loss. Four of them were asymptomatic and didn't prove to have sensorineural hearing loss. Three of the symptomatic kids with congenital CMV had no sensorineural hearing loss at the time.

And of those with sensorineural hearing loss, six had isolated hearing loss. And four had additional symptoms.

And I'll maybe keep this slide up. While we talk about some questions. But here this shows the experience to date and Lauren Gallagher and Dr. Jess Dunn have done a lot of work so we can show this today 93% of babies born have been screened. There have been 182 so .4% have -- .14% have tested positive in dried blood spot sample we have had 16 cases in babies where CMV was negative on urine PCR so those could show false positive DBS screens I will say in two of those cases it turns out they were true positive but the urine PCR was negative. And here you can see the breakdown about 82% were asymptomatic, 15% were symptomatic and again you can see the breakdown in the end here in terms of who had sensorineural hearing loss and who didn't. The last thing I'll show here is there are six cases. So 3% of those who screened positive where the parents did find further evaluation.

So I think I've seen questions come up around this so I just wanted to highlight this.

>> ALYSON WARD: Yes I think that's excellent thank you it's definitely good to see this flowchart and what's happened since the universal screen has taken place. Or been kicked off. So one of the questions we actually had as an -- there was an email yesterday so this is someone that does work in a hearing program in Ontario. And was wondering for clients who have been identified with hearing loss differences and have received a negative CMV screen, would you recommend a physician to request further testing to roll out CMV?

>> PRANESH CHAKRABORTY: Yeah, so I think that's -- that's a question without a black-and-white answer. I think it has a bit to do with the type of hearing loss. It also has to do with the age of the baby at the time. You know, certainly before we started this, one of the reasons we started thinking about this was we were often getting the question from our ENT colleagues, sometimes genetic colleagues, infectious disease colleagues, to go back and test the dried blood spot because they were trying to care for a child who had permanent hearing loss and was too old, for example, to go back and try to understand whether they had congenital CMV.

So I think it's a bit of a case-by-case basis. But given the known issues. And I think our experience you know demonstrates that sensitivity is an issue and is likely a significant issue for dried blood spot based ascertainment but if the baby is young enough consideration of CMV as a potential etiology is still important.

>> ALYSON WARD: Excellent. Thank you. And then the next question is, can you please talk more about CMV DNA? That is not a term that this attendee has heard

before.

>> PRANESH CHAKRABORTY: Yeah, so when you're looking at testing the dried blood spot what you're looking for is the genetic material from the CMV virus itself. And that genetic material is DNA.

So when people talk about doing a CMV PCR test, that PCR is looking for DNA of the cytomegalovirus itself.

So when we're looking at testing the dried blood spot, what we're looking for is that DNA from the cytomegalovirus in the blood spot.

>> ALYSON WARD: Great. Thank you. Thank you so much, Dr. Chakraborty. We really appreciate you taking the time to present to us today. Today's presentation will be -- has been recorded. And will be uploaded onto infanthearing.org as well as CMV.usu.edu.

Just a quick reminder I'm going to click through some of the things that Dr. Chakraborty wasn't able to get to.

Just a reminder to save the date for August 22nd through 24th next year and come and join us in Ottawa. And if you would just please take a minute, if you click on this link right here, if it doesn't work for you, I've also -- you can copy and paste the URL. It's just right underneath the link if it doesn't allow you. We've had some issues with people have firewalls where it won't let you into the evaluation. So if you would just take a minute and evaluate the information shared on this webinar as well as if you are looking to get a certificate of attendance, please go ahead and follow this URL. And in the meantime, thank you so much, again, for joining us. And have an excellent weekend.