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NEWBORN HEARING SCREENING FOR FRAGILE X SYNDROME AND OTHER DEVELOPMENTAL DISABILITIES
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>> OPERATOR: Hello and welcome to "Newborn Screening for Fragile X Syndrome and Other Developmental Disabilities". My name is Anna Costalas and I'm the resource and dissemination manager her at AUCD I would like to thank you all for joining us today before we begin I would like to address a few logistical details first we'll provide a brief introduction of our speaker after the speaker's presentation we'll have time for questions because of the number of participants send your questions during the presentation in the chat box to the webinar console you may send the chat to the whole audience or presenters only we'll compile the questions and address them at the end please know we may not be able to address every question and may combine questions this entire webinar will be recorded and available at AUCD's Website following the webinar there will also be a short survey evaluation at the close of the webinar we invite you to provide feedback on the webinar and also to provide suggestions for future topics. Please join me in welcoming Dr. Mary Beth Bruder Chair of the AUCD Early Childhood Special Interest Group. Mary Beth.

>> Thanks, Anna, welcome, everybody. This is our monthly Special Interest Group webinar. And before I introduce our esteemed speaker let me remind you we have the AUCD national conference next month the early intervention group will meet on Monday at noon to 1:30 our next webinar after this will be in December since we'll be at AUCD in November and in December we'll be bringing a topic about the latest research on service coordination today you guys are in for a treat I was very lucky to have heard Don Bailey present on his latest research at an international conference in Australia a couple of months ago. I've known Don for a really, really long time. And had always been an admirer of his and also he has been a great teacher to me and everybody else in the field. He had been at North Carolina Chapel Hill where a lot of his early

intervention work began and continued when he became the director of the frank Porter Graham Child Development Institute.

And after he left that, after an he is schemed career of writing research articles as well as textbooks that are still used in the field at least by me when I go back and I think there's still timeless information in there, he then moved over to focus on his passion, which is looking at Fragile X syndrome and some of the implications of screening, early identification and then early intervention.

He has a number of partnerships and lots of funding still. But he primarily is focused on this one area and has really brought to light a number of challenges both ethically and then programmatically.

So with that, I turn it over to Don and questions will be at the end.

>> DR. DON BAILEY: Great, well, thank you, Mary Beth. And welcome everybody, good afternoon. I'm looking forward to having a chance to share some of our work -- recent work with you. And talk about what I really think are some of the big issues that are facing us in the developmental disability field and especially related to early identification of children you know through -- I'll talk about newborn screening but there are a broader set of issues about when and how we identify children with disabilities.

So as Mary Beth mentioned I was at the University of North Carolina for most of my career or for much of my career. In 2006 I left and moved to RTI International, where I am now. RTI is a large nonprofit research institute located in Research Triangle Park North Carolina.

The picture on your screen there is our new headquarters building. And I and my team are located in that building. RTI is very large we have offices all over the U.S. and around the world. And do work in a variety of different areas. Someone asked me one day if RTI did anything besides disability work. And I just said, you know, I'm just one little cog in a very big research enterprise here. We've got over 5,000 employees doing a variety of different things.

But the great thing about RTI, so it's a nonprofit. It's all funded by external grants and contracts. So they let me do -- focus on things that I want to do. And the tagline for RTI is improving the human condition. And certainly what we're trying to do and what everybody on this call is trying to do is improve the human condition in a subset of the population that we are very familiar with.

So just very quickly to make disclosures about our primary funders. So our core funding is from the NIH, we have two large awards, one from the National Center for Advancing Translational Sciences. And then one from the Eunice Kennedy Shriver National Institute of Child Health and Human Development we also are partnering with and receiving funding from a number of patient advocacy groups. Our work has garnered a lot of interest in people who have their favorite disorder that they would like to study. And to have -- and have -- and often have children that they would like to be

identified earlier.

And so we get funding from a number of those sources. It continues to grow.

The John Merck fund is a family fund that provides support for much of our Fragile X work. The only commercial entity here is Asuragen which is a small diagnostics company in Texas. And they have been contributing reagents and equipment for our Fragile X newborn screening world so I lead now the Center For Newborn Screening Ethics and Disability Studies and we were just chatting about this a little bit before the call started. Newborn screening and I'll tell you more about what that is and some of the issues surrounding it today is all about the earliest identification of children with health problems. But as a public health program, it also comes with a series of ethical issues. And those ethical issues are rather than being resolved are growing. With the advent of technology, with whole genome sequencing, with uncertainty about predictive genomics and a variety of different treatments that are out there and the very cost of those treatments. There's a lot of important ethical issues around social justice and parent preferences and who knows what and when we can disclose things to families so that's a part of what we do. And then Disability Studies is our traditional work on studying the nature and consequences of various disabilities so my favorite disorder is Fragile X syndrome and I've been studying that for many, many years. But we have many disorders we're studying as well and a longitudinal study now funded by NIH to look at the development of babies affected by congenital zika syndrome in Brazil.

So when I was at UNC as Mary Beth mentioned I directed the Frank Porter Graham Child Development Institute. It was an interdisciplinary institute. We had people from psychology and medicine and special education and a variety of other fields.

But this center I have now is really about as diverse from a disciplinary perspective as I've had the opportunity and privilege to work with so the topline are the MD or PhD level folks on my team with -- I have two licensed psychologists, I have three licensed genetic counselors. People are training in bioethics and public health and Early Childhood Special Education family studies. And then I have a laboratory team, as well. Brook and Veronica are relatively new to RTI we didn't have head shots for them for this particular presentation and I'll tell you a little bit about the lab that we're now running for our own newborn screening work.

It's been a great team. And I just -- it's so stimulating to really think about these issues from so many different perspectives.

So RTI does not provide any clinical services. So we are doing screening for certain conditions under research protocol. But we don't do any diagnostic work or follow-up work except for under our research protocol. So we're partnering with three local universities, Cindy Powell is a medical geneticist at the University of North Carolina at Chapel Hill. Michael Cotta in a neonatologist at Duke University Nancy King is a bioethicist at Wake Forest Baptist Medical Center so they are our primary clinical and ethics partners. Then we have also a business associate agreement and

formula partnership with the North Carolina State Laboratory of Public Health. Scott Shown actually was on my team until about a month and a half ago when he became director of the North Carolina State Laboratory of Public Health. So it's a great thing for North Carolina and for us long term to have him there in that partnership.

What I'm going to do is really try to compare and contrast the world of early intervention as most of us on this call I think know it to the world of newborn screening with early intervention, which is very really non-disease focused. It's really focused on kids with documented delays and disabilities. But not necessarily the primary focus isn't on diagnosis the particular cause of the disability although that's certainly a part of it. The treatments and early intervention are certainly interdisciplinary but they are primarily non-medical treatments.

There's special education, physical therapy, PT, OT and so forth newborn screening is really the reverse it's a very disease specific world where screening is conducted for only particular disorders with certain criteria that I'll describe in a minute.

And probably cure oriented is the wrong word to use. But certainly treatment oriented with a focus on specific treatments that have to be delivered early, very, very early in life.

So I'm also going to raise some broad questions based on that about presymptomatic screening and treatment because really most early intervention is done either with children who have documented delays or who have a condition like Down syndrome where we know there's likely to be delay newborn screening is done with babies who seem completely normal what we call presymptomatic screening and the fundamental assumption there is you want to pick up these children before symptoms appear because treating them before symptoms appear is much more effective than treating them later.

I'll talk about Fragile X syndrome as an example of a lot of the challenges we face in early intervention. And how that -- and how Fragile X syndrome fits or doesn't fit into the world of newborn screening. I'll describe briefly Early Check which is a newborn screening research project and I'll raise questions about the role of early intervention in maybe not a world grow but a growing world of medicalization of treatment.

Finally I'll ask whether and how we can use early intervention as we know it to justify newborn screening for developmental disabilities.

I'll come back to all of those throughout the presentation.

So first what is newborn screening probably most of you on the call know something about it or maybe a lot about it.

So fundamentally newborn screening is testing children at birth for serious health problems that are not obvious cannot be detected through clinical presentation this photo on the right is a baby born as a result of congenital zika infection. You don't need newborn screening to pick this up. These babies are clearly -- this is a pretty good looking baby but there are some that are quite severely impaired with severe

microcephally and other birth defects. so newborn screening wouldn't be used for this disorder, wouldn't be used for Down syndrome, for example.

Testing Children at birth for serious health problems that can't be detected through clinical presentation and clinical presentation when it does begin might not be so specific to enable a quick diagnosis.

The newborn screening is usually done on dried blood spots I have a picture here of a card that's used in some states. So within about four hours of birth or shortly thereafter a phlebotomist or nurse comes in and either does it in the room or takes the baby out and does a heel stick and this leads to -- and puts at least four and sometimes up to five or six dried blood spots on the card. Along with identifying demographic information and barcode and that's sent to a state lab. And the state lab tests those dried blood spots for whatever disorders are included on their newborn screening panel.

So for newborn screening you have to have data demonstrating that treating the condition as I mentioned earlier before symptoms occur results in significantly better outcomes than treating the condition after symptoms become obvious so if it doesn't matter if you can do the treatment and it's just as effective as 6 months or 9 months or 12 months of age once a diagnosis occurs then you would not do newborn screening. It's only done for -- when you have evidence of presymptomatic treatment efficacy and it's essentially considered a medical emergency that these are babies you don't -- if you don't treat them very, very quickly they could die or they could suffer some serious impairment that's irreversible.

And of course a final criteria would be that follow-up and treatment programs are available and can be implemented so you certainly wouldn't include a disorder in newborn screening if you could not do follow-up and treatment as would be indicated. So newborn screening policy in the U.S. it used to be 30 years ago it was like the Wild West every state had its only panel of disorders and you might have 2 disorders in one state being screened for and 10 in another and 20 in another so there's a lot of inequity across states. So there's the March of Dimes and the Government Accounting Office and others did big -- there are a number of reviews published basically saying this is not right.

And something needs to be done to harmonize screening across the nation.

But screening is under the purview or prerogative of state health departments and the Federal Government is very reluctant and maybe even can't mandate the state -- that state health departments do certain things so the way they try to address this and did address it was by establishing a National Advisory Committee on heritable disorders on newborns and children. So I served as a voting member of that committee for six years. It was really a great eye-opening experience. Parent advocacy groups or researchers or clinicians nominate disorders for the committee to consider. Committee does an initial review. If we think there is enough evidence to -- if there's at least some evidence out there that's worth doing a full-blown formal evidence review then we'll

move it onto that phase otherwise we'll send a letter I say we I'm not on the committee anymore but a letter will be send sent back to the nominators telling them where the gaps are they need to address.

So there's this rigorous review process that usually takes 9 months to a year to happen.

And then the committee makes a recommendation. That recommendation goes to the DHHS Secretary who then makes the final determination of whether a condition should be on what's called the RUSP, the Recommended Uniform Screening Panel then it's up to the states to decide. This has really worked, though, it has led to much more harmonization of screening across states. Still some variability but states really recognize that if a national committee has recommended they screen for the disorder it puts them in some jeopardy if they are not screening for those disorders. But states still decide and every state has its own model where sometimes it requires legislation, sometimes it's a state Advisory Committee. Sometimes the state health department can just do it. There's quite a bit of variability around the country. There are currently 35 disorders on the RUSP. And states are gradually implementing newly recommended conditions. So usually it takes anywhere from 3 to 5 years once a disorder is on the RUSP for states to gear up and do it -- it depends considerably based on the states.

So there are a lot of disorders that won't make the RUSP in the near future. There have been 10 that have been nominated since the committee was formed either not initially recommended or sent to evidence review and you can see the names of those, you may be familiar with some of those disorders. The most recently approved one was spinal muscular atrophy I'll tell you a little bit more about it in a minute.

You can see it's also first on the list of not recommended. So SMA was initially recommended was -- was nominated in 2008 but wasn't approved until 2017 so this shows the high bar for evidence and length of time sometimes it takes before the committee has enough evidence to make this recommendation. Congenital cytomegalovirus infection was the most recently nominated back in April but it was not sent for evidence review.

Major reasons for not recommending disorders to either be sent for review or once they are reviewed still not to be included on the RUSP are first no accurate and cost effective screening test that's the first thing. If you don't have a screening test that can be done on blood dried spots it's very accurate and not very costly then there's no other questions that are asked you have to have that test first. States usually err -- they want it to be highly accurate in terms of identifying all babies with the disorder. Because most tests are not completely accurate states often set a bar that -- or a cutoff that's higher or lower depending on what the variable is than necessary to make sure they catch everyone so they want no false negatives. They don't want any baby to be missed so there are often a lot of false positives as a result of newborn screening so

one of the ethical questions is how many -- what's the tolerance for parents for false positive information, how fast can you get the diagnostic information and certainly with this Internet world that we have now once parents get a screen positive test they will go on the Internet and find out all of the bad things about that disorder. Which the child may or may not have but the screening test is the first criteria. A second criteria is it will be too complicated or expensive so congenital cytomegalovirus infection there are a lot of kids screened for that but the follow-up is complicated who gets treated who gets under surveillance protocol and who will never need treatment it's very complicated so it's a difficult system to implement with our current knowledge there's always required pilot study data and the final thing I mentioned earlier on data on pre symptomatic treatment efficacy these committee meetings were public meetings so they are pretty interesting context where parents bring photos of their children or bring family members and really standing up and making very passionate pleas to include their child's disorder or their favorite disorder in newborn screening and they would basically stand up and say you guys are going way too slow.

The committee would usually -- usually recommends a condition once every one or two years. The advocates think this pace of expansion is way too slow and children are suffering and dying as a result. States have the opposite perspective for the most part they think the pace of expansion is too fast to add one or two disorders -- to add a disorder every one or two years for many, many states is just a heavy lift for a variety of legislative and financial reasons. So the committee is in the middle of this very interesting world. And trying to make rational decisions about what is the right kind of evidence to advance a public health program. Essentially it's a mandatory program so most states newborn screening is done without consent you can opt out for a certain reason for moral or religious reasons but by and large it's done without consent so states would be very reluctant to -- and the committee would be very reluctant to recommend a disorder for screening under essentially a mandatory public health model. They don't want to jeopardize regular newborn screening by including disorders that are more questionable.

But most of these disorders are very rare. So they are caught in this classic Catch 22 situation where screening can't be mandated without evidence. But screening is needed in order to gather the evidence. So if you have a disorder that occurs 1 in 10,000 or 1 in 50,000 or even 1 in 100,000 children how are you going to find enough babies with that disorder to do clinical trials to demonstrate treatment efficacy especially presymptomatic you can find babies who have the disorder but they are usually older what you need to do is find them presymptomatically so it requires large scale screening programs under a research protocol. In a seemingly rational world where we have this committee and process and it's rigorous and it's rapidly changing, there are more than 3,000 known genetic causes just of intellectual disability and if you think about other disorders that are health related they have the potential from a genetic perspective to

identify literally thousands of disorders so you contrast that with the 35 that are currently on newborn screening there's a big gap there. Methods now exist to detect a lot of these disorders before symptoms appear. So it has happened before in newborn screening technology and technology advances they are likely to drive change before we're ready for it from a clinical or ethics perspective.

So also there are new and sometimes very expensive treatments that promise hope for a cure at least stopping disease progression I'll give a couple of examples of that. Disease specific advocacy groups are becoming powerful change advocates and these factors are really pushing for rapid expansion of newborn screening. So what's the role of those of us who are in early intervention world what's our role and hue does that compare and contrast to this and how do we make decisions and how do we fit into this and ultimately as early intervention as I'll bring this up in a moment is early intervention a treatment? As newborn screening would be -- thinks about treatment.

So I won't belabor this slide but just say there are a lot of patient advocacy groups out there about -- you name a disorder, there's usually more than one advocacy group. They don't always get along with each other. But they are becoming very savvy about what they want to accomplish some focus heavily on funding raising money to support research. To find a treatment for their disorder others put their energy into screening or other public health changes but it varies from disorder by disorder but they are becoming very powerful advocates for change new methods as I mentioned are constantly evolving to identify high risk infants before symptoms appear. The technology has always been a major factor in newborn screening. 30 years ago mass spectrometry at the university the -- this was a technology where you could screen for 30 or 40 disorders. It's the one at one time.

And really at about the same price.

So that really changed newborn screening, opened up the door if you can -- with multiplexing disorders in one panel or in one approach. Then that eliminates the technology barrier. Eliminates the diagnostic barrier. And so what you then have to focus on is the treatment question.

There have been a sequence -- genomic sequencing you've been -- everyone has been reading a lot about that I'm sure. NIH funded four centers to look at the potential implications of newborn sequence can and genomic medicine and public health and we partnered with UNC and one of those projects this is Joe Pivin and colleagues recently published studies where they showed that you could do neuroimaging of high risk 6 month old infants these are infants siblings of children with autism, you could predict with almost 100% accuracy which child would ultimately have a diagnosis of autism at 24 months of age.

So there's a whole -- my main message here is through either what they would call microarray analyses or panels or through genomic sequencing or through other kinds of imaging methods we have the capability to identify many more children than we have

the capability or the understanding of what to do with them.

So the treatments are really changing and the most ones are metopoetic stem cell transplantations and they are really changing the meaning of that spinal muscular atrophy is a good example of this it's a recently disorder approved for newborn screening it's caused by mutation in a single gene.

It results in insufficient protein production that would maintain the survival of motor neurons. So these babies as this would be classic for newborn screening these babies look -- they are completely normal at birth and progressing pretty normally from a parent perspective although underlying symptoms damage is already happening. Usually about six months of age is when the symptoms really become apparent and pretty quickly after that babies are diagnosed. Then traditionally though most babies who have Type 1 spinal muscular atrophy pass away if untreated at about 2 years of age. There are more mild versions Types 2 through 4 determined by a copy number of a second gene and this raises fundamental questions in newborn screening as well if you identify a baby who has -- who might develop a very mild version of spinal muscular atrophy as an adolescent should the parents want to know that information and should treatment occur earlier for those the history is for most of its life these children didn't have any treatments. It was primarily supportive care palliative care breathing machines because of the severity of the disorder a number of years ago American College of Obstetricians and Gynecologists recommended SMA carrier testing of women and men. So that you would know if you were an SMA carrier. And because the only real treatment was to try to prevent the disorder.

Then a couple of years ago a medicine called -- a therapeutic a targeted their particular called Spinraza or also known as nusinersen it's an oligonucleotide was approved and turned out to be quite effective in stopping the progression of the disease. It's not a cure. But it slows or stops the progression of the disease at least in children as far as we know so far up to about two years of age and then this past spring there was a gene -- one of the first gene therapies approved, was approved, Zolgensma, so there are now two very big treatments out there. For this disorder and it's only going to grow. In terms of what we know about other disorders.

The problem is I can't remember if I have a slide on this or not but these are very expensive treatments. So Spinraza requires two spinal injections in the first year of life and then one for the rest of each year for as far as we know for the rest of your life. They cost about $375,000 per injection. And so you're talking about you know $800,000 the first year and then close to $400,000 subsequent years.

The gene therapy is being marketed now at $2 million. This is a -- it's supposed to be a one-time treatment that basically cures the disorder but they haven't been -- there haven't been long-term follow-up studies to really know the answer to that so this of course raises big questions about ultimately what are we going to be able to afford as a nation and how do we make those decisions about social justice. So Biogen is the

Spinraza company they are the company that has Spinraza about how you can live a great life what can Spinraza unlock? Then Avexis who developed Zolgensma and Cure SMA has provided a lot of support for them and been big advocates for newborn screening for SMA and this is why it got ultimately approved by the committee.

But that's not true -- but all disorders are not the same so for some disorders, certainty of risk can be a challenge. So another more recent disorder included in newborn screening is called X-linked adrenaleukodystrophy. So this is an X-linked disorder called by mutation in a single gene as a progressive loss of myelin that surrounds the brain and spinal cord nerves here usually the symptoms appear in boys primarily between 4 and 8 years of age. So you have to do very long chain fatty acid and ABCD1 genetic testing that can confirm the diagnosis but it can't confirm the disease state. Here is an example of a disorder where you've got all of the genetic markers all of the biomarkers for the disorder but you might not have the symptoms of the disorder.

So that -- so what is required then is and imaging until -- and imaging can detect the disease before symptoms start to appear.

The treatment history here, this is -- you probably heard of and seen the movie probably about Lorenzo's oil still unproven corticosteroids when there's adrenal insufficiency has been proven for a number of years bone marrow transplant is now the treatment option of choice but when you only do that when the MRI starts to show lesions and gene therapy is certainly going to be available in the near future -- in the future but it's still experimental.

But here this is a situation where parents really have to start worrying, again, worry and wonder about when, when is this going -- disease going to present itself in my child? And then bone marrow transplant is not a minor operation. It can be fatal for some children. So there are many difficult choices there to make.

In the interest of time I'm going to skip this slide. Only to say that we've done a lot of studies recently of parents' tolerance for uncertainty about -- Brook and Holly on my team are very interested in this because how we deal with uncertainty is really -- varies across people and so some people will want very certain results and others are willing to tolerate more uncertainty.

(Background noise.)

>> DR. DON BAILEY: I'm hoping everybody can still hear me, I'm hearing a lot of background noise. But I'll just move on so some important questions are you know just because we can identify the causes of health problems does that mean we should identify them and when. How much evidence is required and will it need to be provided for every disorder?

How certain must we be in disease prediction to justify screening? And how do cost and social justice factor into decisions about screening?

So let's talk about Fragile X syndrome for a moment. Most of you probably know

what it is. It's the most common known inherited cause of intellectual disability it's an X-link single gene disorder and called a trinucleotide expansion disorder and inherited disorder that can involve many family members it's initially discovered as a chromosome problem the arrow there's a picture of the X chromosome with a little piece that looks like it's pinched that's why it originally got the name of Fragile X in 1991 the gene was discovered so it's a single gene disorder we know exactly where it is and exactly how to detect it.

So you can have three general states here. You have the normal state would be -- it's what's called a CGG repeat expansion disorder. So most people in the world would have -- well the average CGG repeats at this gene would be about 29 or 30. As long as you're less than 55 you would be considered normal. With respect to Fragile X 55 to 199 you're considered to be a carrier of Fragile X syndrome once you have more than 199 repeats you're considered to have the mutation and all of the disorders associated with Fragile X syndrome more recent research are showing that these boundaries are more blurred and not as clear as we once thought so I'm sure that a child that has 195 repeats will certainly have developmental disabilities so this gives an example of issues that come up for screening about where do you set the cutoff and what do you report?

A lot of research I'm not going to try to describe this slide except to say you think a single gene disorder was pretty simple. But there are really lots of complicated pathways for the single protein because it seems to interact with lots of other proteins in a different path and in the -- in biology. So within these paths there's a lot of potential medication targets so people have tried a lot of them. So far nothing has really turned out to be the big treatment for Fragile X. A lot of the clinical trials people thought would be successful have failed so we do not have a medical treatment for Fragile X we only have symptom treatment there still are things that are being tested. But we're a long ways from having a medical treatment for Fragile X or gene therapy for Fragile X. That would make it qualify for newborn screening in that way it's difficult to diagnose in the early years we published several papers on this the most recent one it's hard to believe was around ten years now we are collecting a new round of data at the moment this shows the average age of Fragile X syndrome is around 36 months of age the bottom line shows the average age however of someone first becoming concerned about the child and that's usually around 9 to 14 months of age that's usually apparent the middle lines show when a delay is confirmed by a professional and services begin. But for a lot of reasons the diagnosis of Fragile X still doesn't occur until much later. So the problems with that are it's a long and extensive what people talk about diagnostic odyssey most children don't get intervention during the first two years of life we found about a third of families who have a second child of Fragile X even before the first is diagnosed.

So we started writing about this, good grief, now 25 years ago.

I wrote some papers about let's think about how we can think about the situation. We can do newborn screening for Fragile X. Well back then I was completely naive as to what newborn screening was all about. I didn't realize the criteria, I didn't realize it's context its nature within a public health program.

And people laughed at me. People from the public health community said well that's crazy what's the treatment I would say well we have early intervention they said well where is the evidence that early intervention makes a difference for this particular disorder? So this is again -- you have to have disorder specific evidence. Not generic evidence. What's the evidence that newborn screening -- that early intervention for Fragile X syndrome would make a real difference in childrens' lives especially presymptomatic treatment so that sent me on a long path of exploratory research realizing that we were going to need to understand the situation a lot better before we could move the needle on early identification.

So you know should it be identified through newborn screening it's a good example of a disorder with no medical treatment that needs provided early but a lot of us say it would benefit children and families but it's a case of a lot of complicated clinical and ethical issues things like should reproductive risk and cascade testing of other family members testing, extended family factor into newborn screening policy decisions right now it's not considered but only a benefit to the infant is access to early intervention considered treatment? And what benefit would need to be demonstrated from early intervention. I'll show you some data in a minute. But how much would we need to move the needle in developmental progress before people would say yeah that's effective and we should be doing that. There are tests as I mentioned earlier there are questions about what are the cutoffs for screening positive cases, complicated ethical questions about whether to report carrier status because we know that carrier adults -- carriers unlike a lot of disorders carriers of Fragile X permutation are also at elevated risk for late onset disorders women are at risk for adult onset primary ovarian insufficiency and a small percentage of women at risk for tremor ataxia syndrome so do parents want to know that their son with -- a carrier baby boy could have a pretty severe tremor disorder in midlife?

This is just one example though of many disorders that are like this and this is an example of the ethical questions that we're facing now and we'll face even more in the future.

We published a lot of articles about this. We started writing about the ethical and legal considerations. We have described the age of diagnosis we have done pilot studies in several projects and I would be glad to send references to anyone who would like to have those. And I'll have my email address at the end of this presentation.

So we have built a research program to help try to solve some of these problems. Early Check is an Innovation Award from the NIH and from a variety of other sources it's a research study we're trying to develop methods to offer free voluntary screening to

every parent who gives birth in North Carolina 125,000 parents for disorders that are not currently part of newborn screening we're usually SMA and Fragile X syndrome as initial prototypes for this.

And we're hoping that acquire data to inform policy about peoples' interest in screening for disorders that are not part of a mandatory system look at what it would take to develop a statewide system of care. Understand the early natural history of screened positive infants and ultimately identify infants who could participate in presymptomatic treatment trials.

I don't have time to go through this in great detail. But basically we have this multi-phase public outreach recruitment model. We have an online permission process. We're trying to do this without sitting down and talking to people about it. We're trying virtual recruitment strategies. EConsent.

For people who give permission then this is a free screening. And the parents don't have to do anything. Through our partnership with the state we are -- we access the dried blood spot they have already collected for children. We then -- my staff, my technicians run these voluntary screening tests. And if there's a positive result then we refer the baby to duke or UNC, depending on the clinical -- on the condition. For confirmatory testing and then diagnostic follow-up treatment and then we provide information, support, ongoing surveillance and registry and helping families get into intervention programs or clinical trials.

This is just -- I won't -- I don't have the video up here to show. But the eConsent has three short whiteboard videos on there that are pretty engaging. It's a great way to get people involved in understanding.

What is unique about early check, it's a collaboration among a lot of different research partners. It's statewide recruitment as I mentioned we're trying to evaluate virtual recruitment methods within that for people who agree to participate in Early Check there's a second consent for Fragile X carrier status. Part of the requirement from the funder is that we have a central IRB so UNC is that IRB and Duke, Wake Forest, RTI and the State Lab all defer.

We have short and long-term follow-up for each disorder we have robust telegenetic counseling program in place, as well.

As I said a major goal is to test recruitment strategies we want to offer Early Check to every birthing parent in the state we need to figure out what is the best begin nation of approaches our goal is 25,000 enrollees per year by the end of 2020 we just wrapped up our first year I think I'll show this on the next slide of studies where Phase 1 and Phase 2 we got about 5,000 families enrolling through these two strategies so we're now having to focus on a much more intensive in-person strategy. Phase 1 every parent got a letter within a week after birth signed by the state medical officer and a brochure telling them about Early Check but they had to take an action, they had to -- first of all they had to open the letter and then secondly they had to go to the Website,

go through the consent process doesn't take that long just a few minutes.

Then we tried a social media campaign. Had paid social media ads those are pretty expensive as it turns out and didn't really move the needle for us very much so now we have multiple hospitals in the community strategies we're working with the WIC program statewide. We're inviting people through patient portal and a variety of other strategies to try to increase recruitment. Ultimately we will have to go to some in-person recruiting and some offices or some of the larger hospitals. But we really have been resisting that because we want it to be statewide.

And at least for right -- so far we've gotten consents from all -- from 100% -- at least one family from 100% of the hospitals in North Carolina and 98% of the counties so we have a statewide reach but we just don't have the numbers.

I don't have time to go through -- I think we want to talk about some other things but we do have a telegenetic counseling program for return of results. And we also have educational web content our team has developed some really great materials for families to help understand complicated disorders, genetic disorders.

Fragile X we are testing an early intervention model so Anne Wheeler and Melissa Rasp the whole team here are doing this this is funded primarily by the John Merck fund so during the first 8 to 12 weeks of life we're providing a modified parents as teachers curriculum. This is 4 to 8 sessions over 8 to 12 weeks then we move into this Phase 2 which is the iBasis VIPP this is children at risk for autism it was developed in the UK and we have modified it for children with Fragile X syndrome based on advice from a number of consultants we're piloting it now this year.

So this would be -- we can't -- because these babies are all -- could be all over the state. We don't have the capability of providing center based programs so it's partly in-home and partly telehealth. We are working on developing an early intervention model. I don't know if I have this -- yeah here it is. We're planning a virtual early intervention center which clearly there's a need to provide families and professionals support for what do you do with children with rare disorders such as Fragile X? We have received some funding to plan a virtual early intervention center through the -- that would support both families and early intervention professionals it wouldn't replace early intervention it would supplement it and support it so it would have four core components, telegenetic counseling. We have remote developmental assessment capabilities where we can actually use through video streaming we can watch a family. We can instruct them in presenting stimuli to children we can use remote monitors. So it's pretty cool and interesting way to do -- interesting way to do developmental assessments of children we are studying the PiXi and early intervention program and possible applications of mindfulness training for parents using telesupport so we're excited about this as a potential add-on to early intervention. Like I said we have planning grant money. But sustaining something like that with the business model for it is going to be a challenge for us.

One of our long-term goals is determine whether identifying disorders such as Fragile X syndrome at birth makes a difference in the lives of children so is it greater than that obtained if we wait until symptoms appear and children become eligible for early intervention at age 2 this question will be difficult to answer because we're not going to have enough children to have a true control group we certainly can't have a no treatment group. We still don't know the natural history of many aspects of Fragile X and need to figure out what outcomes should be used as a litmus test for developmental screening we can say progress can be one of them if you ask parents of older children what's the No. 1 treatment outcome they want is reduction of behavior problems associated with Fragile X so if that's the goal what do you do during the first year of life that might reduce behavior problems in adolescents?

We've been working on a collaborative paper involving researchers from around the country who have sent us the data on males and females with Fragile X. And the females are in red and males are in blue. Basically this over the first five years of life and basically this shows a couple of things. First of all, a tremendous variability. It shows the girls are more mildly affected than boys and shows that there are some children like some boys who make virtually no progress over the entire five years of early childhood and others that are pretty close to the normal development line and some in between average growth rate for males is about half of that of typical development females are about two-thirds of typical development the question is which one should we be trying to demonstrate benefit for all of these children how much would we be needing to move those growth rate lines to show evidence of benefit if we move the growth rate of males from 0.47 to females to 0.62 would that be enough that would be a statistically significant change but you can see the line is still well below normal development so no one has ever used behavioral or developmental outcome as a primary endpoint and early intervention as the treatment mode for newborn screening. So this will be interesting to see how this goes.

And of course what outcomes should we expect. As I mentioned, you can have -- we have studied all of these things. There's a lot of things that go along with Fragile X ranging from self-injury to sensory issues to developmental delay so which outcome will be -- where will you hang your hat in terms of saying here is the one we'll work on and through earliest intervention and if we can change it then we can justify newborn screening.

So the big questions for us will we ever be able to say with confidence that early intervention is so powerful that it's sufficient to justify newborn screening. Will we have to answer this question for every disorder? You think about Angelman syndrome or any disorder that ultimately down the road you could identify in a newborn are we going to have to have treatment trials for each one of those disorders that's the current model right now. I just don't see how that can be sustained given the changes in technology and the push by efficacy groups. I think that we're facing a time where we're going to

be having to make some very difficult decisions and it can't be one-off decisions on a disorder-by-disorder basis. So just a few concluding thoughts here.

You know I'm -- my training and background and professional identity is in early intervention. So I'm a strong believer in early intervention there's always going to be a need for early intervention even in this world of new treatment and medical discoveries and technology and so forth. But having said that, the rapidly changing landscape of gene discovery and medical treatments is certainly going to influence what we do.

So for us I think we first of all need to be aware of the power of a diagnosis for families. Most of you know that already. That even when families are getting services most of them still want to know why did this happen? What's wrong with my child? So for most families when they do get a diagnosis -- well, I can't -- I don't know if I would say for most. For many families the diagnosis provides a sense of closure. Okay now I get it now I understand and we can move on to services. For other families it opens the doors to many more questions about especially if there aren't -- if it's for later diagnosis for a disorder that's not a part of newborn screening for which there aren't treatments available or the treatments are very risky or unproven. But that diagnosis is a powerful thing. And I'm not talking about a diagnosis of delay but diagnosis of the cause of a child's delay.

So second thing we're going to certainly need to be able to do is learn how to support families who are dealing with uncertainty. Genetic testing in general is going to identify children with genetic abnormalities that may or may not lead to clinical problems, now most of them will but there are going to be a lot of gene mutations that will have no negative impact on anybody. And there will be a lot that will have negative impact on some people and not others. And how you predict which people are going to have the ultimate clinical symptoms and which ones don't is very hard so we always -- already see many examples of that. So learning how we support families dealing with uncertainty I think it's going to be a key part of behavior in early intervention roles.

We have written some papers on what we mean by presymptomatic treatment for infants with quote untreatable conditions. And I think there are four components to any good treatment program providing information so making sure that families have access to as much information as possible and then that it's accurate information. We have worked really hard -- Fragile X has been around for a long time but people -- the name is terrible. People don't understand why it's called Fragile X. What does that mean? Is my baby fragile health, fragile bones? So -- and then there's -- you can get -- for a lot of these disorders you can get bad information about questionable treatments. Things that have been tried, parent support groups. Websites. There are chat rooms where people can talk about all kinds of things.

So helping families have access to accurate and understandable information. Access to formal and informal support.

Surveillance. And especially if -- going back to dealing with uncertainty, a

surveillance program would be one where children are assessed periodically. There's a couple of things. First of all it will tell you when development might be going in the wrong direction and gives parents some reassurance that someone is watching and ready to provide the next thing, which is preventive and responsive treatments.

We're going to need to figure out what is meant by prevention, preventive presymptomatic early intervention program. I think we know a lot about responsive parenting and good environments and so forth. But general things that we can talk about as a presymptomatic treatment. But are there specific -- are there condition specific presymptomatic treatments that early intervention providers can provide. That is an interesting question.

We're all going to have to develop partnerships with disease specialists in the medical community and finally we need to know that most medical treatments are not going to be perfect.

Children are still going to need special education and early intervention services for many of these disorders because none of the almost -- except for potentially for gene therapy most of the things that are done for children and families are not -- for children are not curative so families are going to need ongoing support.

So this is my -- I'm sorry; I probably talked too long and didn't leave enough time for questions. This is my email degrees, dBailey@rti.org here is the Website for Early Check if you would like to check it out. And we have a couple of moments here I think if anybody has any questions I would be glad to try to answer them.

>> Great thank you so much, Don. Well, we had one question. (Chuckles).

>> From Sally Porter I think in the infancy period how do we report results to carriers as adolescents and young adults wanting to make informed reproductive decisions.

>> DR. DON BAILEY: Right. So we don't really do work with older -- in terms of reporting results to carriers there's a group at Duke, Allen and others have done really some great studies around that. And kind of the general thinking is that people -- people are afraid to share results with adolescents. But there's findings have shown that adolescents for the most part really want to know this information. They get mad if you are -- if they say wait a minute you knew this about me and decided not to tell me? And certainly of course the question is when.

Should they be told as -- when they are in elementary school. Should they be told when they become adolescents? They certainly don't want to wait until they are you know about to get married.

So if a family -- excuse me; if a family knows then there's some pretty important things there.

I think screening is going to be a very different kind of situation. Certainly prenatal screening and preconception carrier screening are more and more being offered. In

fact when we ask parents of children with Fragile X syndrome what -- if they only had one time to learn about Fragile X when would it be, the vast majority choose preconception carrier testing. They would like to know before they start having children. So we don't have a public mechanism for that. Newborn screening is the only true population based way to test everybody for certain disorders. Anything prenatally is going to end up being -- for people who want it and who can pay for it so it's not going to be universal. We're going to be facing some big challenges with that in the future.

Is there a role for quality of life measures along with developmental measures? Of course.

Quality of life is -- well, depending on how you view it and how you measure it, it's a subjective phenomena. And so ultimately you could -- to give an example there's some disorders where you could screen, you could treat, crab A disorder would be an example of that.

But children are still very, very severely affected so there's some pretty tough ethical issues about quality of life. And whose quality of life are we talking about? Are we talking about the child's quality of life? If it's pain free? If they are developmentally more advanced? So yeah quality of life is important. But it has not typically been used as the primary outcome for newborn screening evidence. Because it's just so hard to measure in an infant.

>> Great. Thank you so much for your wonderful presentation. Thank you everyone who attended this webinar has been recorded and will be archived at the webinar library at AUCD.org. Please take a few moments to complete the survey that will pop up on your screen when I close out. Thank you, again, Don for a wonderful presentation. Have a great day everyone.

>> DR. DON BAILEY: Great thanks for inviting me and again feel free to contact me if you would like any further information.

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