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AIR-P GENETICS RESEARCH NODE WEBINAR

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>> MADELINE HALEY: Hi, everyone. We can go ahead and get started. My name is Maddie Haley, and I want to welcome you all to the webinar series for the Autism Intervention Research Network on Physical Health, the AIR-P. Thank you all for joining us today.

Because of the number of participants, your audio will be muted throughout the call. However, you can submit the questions at any point during the presentation via the chat box on your webinar console. The entire webinar is being recorded and will be available on the AIR-P website, airpnetwork.ucla.edu. There will also be a short evaluation survey at the close of the webinar. We invite you to provide feedback and also provide suggestions for future webinars.

In the interest of time, let's get started. We first want to acknowledge the Health, Resources and Services Administration as the funding source for the AIR-P. Now, it is my honor to introduce our speaker for today, Dr. Julian Martinez. Dr. Martinez is an associate professor at the department of human genetics at UCLA and the leader of the AIR-P genetics research node.

Please join me in welcoming Dr. Martinez.

>> DR. MARTINEZ: Thank you so much, Maddie.

Today I wanted the start by thanking the AIR-P for the opportunity to share our latest understanding on the role of genetics evaluations in the care of individuals with autism or other neurodevelopmental conditions, and I wanted to clarify as part of the title that even though the title is genetics care in adults and children with autism and neurodevelopmental disabilities, what we're really talking about are diversabilities.

So as Maddie mentioned, this project is supported by HRSA through a grant that supports the AIR-P.

And where we would like to start is defining some terms that we're going to use through today's webinar, including the term Autism Spectrum Disorders, which as we know, encompasses a group of neurodevelopmental differences that include differences in social interaction and communication, but also some stereotyped patterns of behavior, it's fairly common diagnosis is present in up to one in 58 individuals in the U.S.

We know that there are gender biases, and there are not only genetic distributions, but our environmental ones as well. And when we look broadly at what is known to date about the genetic contribution to susceptibility to autism spectrum, there are more than 800 genes and the list becomes broader and broader every day, that each accounts for a small number of cases.

Now, the other term that we wanted to be aware of is developmental delay. Broadly defined as age matched differences in two or more categories of developmental mile stones, that can include language, motor, social, and activities of daily living. The diagnosis is usually made before the age of 5, which is usually when a lot of individuals, particularly children, are first identified.

And autism spectrum conditions can overlap within this distinct group of neurological presentations.

So, in many instances, we actually see or observe the developmental delay that can then evolve into intellectual disability in some cases associated with autism spectrum phenotypes as well, and that we can call a combined diagnosis, and may represent in some cases more severe instances of autism, and that other symptoms and other medical conditions can be associated with them.

So when we're discussing the challenges for genetic diseases in general, we have some instances or some information available from large studies that have rare genetic conditions as part of consortia, where we get a sense of the journey to finding a proper genetic evaluation, where 25% of patients end up waiting up to between 5 and 30 years for a diagnosis.

40% receive an initial incorrect diagnosis and about 25% of them end up traveling very large distances to identify a potential specialist that could then reach a conclusive diagnosis.

And in 50% of cases, they receive genetic counseling, but 25% of them were never informed of the genetics at all.

So we call this a diagnostic journey, or an odyssey, where there's a long period between the symptom onset and the diagnosis. And we know that in cases where we look at admissions to hospitals in children that have significant medical concerns, that there's a genetic component or a genetic contribution to those clinical symptoms in about 71% of them.

And there's a significant associated cost associated with those admissions, particularly when there isn't a diagnosis achieved in a timely manner.

So what is it that we really know about the genetic contributions to neurodevelopmental conditions, including autism? And sometimes studying something, a clinical presentation as common as autism provides insight into more rare genetic presentations.

And we know that there is some evidence from twins and familial studies that there's a higher likelihood that they both will have autism when their genetic material is identically shared, than in twins where there are differences among siblings with most of their genetic material.

So that just to begin with provides a likelihood that some of these genetic findings will contribute to the manifestation of symptoms to a high degree.

Now, we know, however, that autism comes in multiple instances. We have cases in which the clinical phenotype is associated primarily with other symptoms. That affects multiple organs. Versus the type of autism that presents isolated, without any other major or clinical concerns.

And we discuss the more complex forms of autism, the term syndromic, not one entity is likely the cause. It probably represents many different causes. And many patients persist with similar symptoms, but their genetic diagnosis can also be very different.

So what do we include as part of a genetic evaluation for autism?

So first comes a clinical diagnosis, and that's actually administered or evaluated bay psychiatrist, psychologist, neurologist, or behavioral specialist, like neurodevelopmental specialist in the pediatrics realm, both in adults as well. Perform a clinical evaluation and use instruments to identify whether there is a potential risk or manifestation of those symptoms.

And then typically, what we suggest is that there will be a component as part of the person's evaluations by a geneticist or genetic counselor to find any other coexisting concerns, whether they're medical or more neurological.

And of course the presence or absence of other physical findings, whether there are congenital concerns or other differences in external features in the body that can give us clues as to whether there's a higher contribution of single gene genetic cause.

So we're making that initial assessment, we're trying to find that is this autism by itself, or is it more syndromic, or associated with other neurological organ systems.

And the intent of pursuing the testing, which kind of follows the initial evaluation with a geneticist to help identify if there is a gene identified, pursue opportunities for family counseling, both for assessing whether other family members are at risk for themselves or their children.

Provide family support and advocacy, because sometimes a genetic diagnosis provides a community where you can find access to understanding the intricacies of how to deal with day-to-day access to care and challenges. And of course, facilitate understanding prognosis and identifying potential physical concerns that may manifest over time, with potentially having some personalized treatments available in a subset of them.

So the idea is to make an impact in the lives of children with rare genetic conditions, and to better understand the clinical course of these conditions by reaching out to community physicians and practices and families to educate them about the utility of this approach.

To provide genetic counseling to address the uncertainty of what caused it and whether it will happen again, which is part of the diagnostic journey. And many times, more than one affected child is born before a diagnosis is made, which may place them on future family planning, and to be able to anticipate potential medical complications like seizures and develop a personalized treatment plan if available and appropriate based on those future comorbidities or coexisting medical problems.

So, a further genetic evaluation, we take a very careful family history to identify whether there are affected siblings or other family members. The prenatal history to ensure that there haven't been any exposures during development or other differences that might have contributed to the symptoms that you're observing in the clinic. The developmental history, because that can be telling about whether there's a pattern of milestones or slow attainment of specific developmental milestones.

And the physical exam, we're looking for external features that might be sufficiently unique or that stand out that might suggest that there might be a pattern that could suggest a monogenetic or single genetic ideology.

And of course, that is coupled with genetic diagnostic testing, something that you will hear about today.

So in general, the features that we feel are suggestive of a genetic syndrome include the presence of one or more major structural abnormalities, where there's a difference in the development of an organ that is sufficiently significant, that affects its function. Three or more minor malformations, and those are differences that might be cosmetic and they might be fairly atypical, but that in and of themselves, don't affect the function of that particular body part.

But that when you start looking at patterns of how they are identified together in one individual, it may be suggestive of a genetic association.

Of course, changes in how your body grows, like failure to thrive, changes in the shape of the face and the head. Additional neurological concerns like developmental delay or intellectual disability. Findings in the skin, teeth, hair, bones, external genitalia, and immune system that can also give us clues as well as changes in behavior and speech.

So what do we know? We know that when you look at genetic information, which as you can see here is packaged in what we call chromosomes, there are about ten-20% of autism individuals are due to known medical conditions that involve some kind of chromosomal imbalance, whether it's a structural problem with the chromosome, where a piece is missing or duplicated.

Or there might be sort of a single genetic change or a single letter change. And of course, there are some environmental exposures that can increase that likelihood. In association with genetic findings.

Now, the way we actually approach this testing in the setting is to pursue chromosomal microarray testing of one of the tests that is offered to individuals. In that case, what it essentially does is count the numbers of copies of genes that you were born with. We all have about 21,000 genes and each gene comes in two copies, one from mom and dad. In boys, there's only one X chromosome, in girls, there's two. But essentially, that's the general approach.

And the idea is that if you have a tool that can monitor each address or each gene in its location in the whole genetic material, can you then tell if there's a missing copy of a gene, or an extra copy of a gene, or adjacent genes. That's essentially what this does, with the use of a chip, this is the earlier version where you could actually see that there was a loss of genetic material when you look at the normal ratio of one, or actually two copies of a gene.

Now, the tools that we have used over time, and now we have much more higher resolution or our

ability to find with more degree of fidelity which genes and which portions of those genes are missing by using microarray tools that are reliant on what are called polymorphisms. These are changes present in the population that might make us different, but not necessarily are associated with symptoms.

And you can use those to then identify whether the copy you got from mom versus dad is there or not. What it does also, it also gives us incidental findings. Like, for example, realizing that there is some coefficient of inbreeding or relatedness in terms of the family members when an individual is tested. Or the degree of consanguinity.

Could be the possibility of what we call a recesssive condition, where by having two copies of the same gene from one participant, you could also have a genetic predisposition. Or by having the same genetic change in both copies, you may actually be predisposed to both copies not working at all.

So what exactly does the microarray check? If you have the chromosomes in mom and the chromosomes in dad and there's a process by which you're making sperm or eggs in order to pass down that chromosomal material, that there can be an instance in which a portion of that chromosome is missing.

And when you pass that chromosome down to the next generation, then you can develop symptoms within the spectrum.

And I'll give you an example of one of these early situations or instances where we had two patients in our practice, one who was diagnosed with autism at the age of 5, but then when she presented in the clinic, presented with significant neuropsychiatric changes that occurred at age 10, that included bipolar disorder and psychotic features.

Then we also had another individual who was diagnosed at the age of 7 with autism, but then by the age of 15, developed significant psychosis that has required multiple admissions to the inpatient psychiatric service. And it turns out that when the microarray testing was performed, that there was a region of chromosome 3 that was missing in one of the copies of the chromosome in both individuals.

And it turns out that that region includes genes that are now known to be important in the communication between neurons and facilitating the signals that promote that interaction between neurons to remain very stable.

And what ends up happening is that this genetic condition, which we call 3q29 microdeletion syndrome, initially associated with autism, because of that pattern of co-association, became now in larger studies that looked at schizophrenia, or individuals with psychosis, both in children and adults.

This microdeletion is actually now recognized as a common associated genetic predisposition for schizophrenia.

So as you can see in individuals that initially presented with autism, the symptoms, what we call the phenotype, evolved over time into a schizophrenia picture. We were able to identify a genetic

predisposition that is now recognized in individuals who only have schizophrenia, but no prior history of autism.

Now, there are some limitations to this testing. It may not detect low levels of mosaicism, meaning changes in chromosomes that are a very small amount in the blood system that may not be identified. It doesn't detect changes in genes that are not associated with a net gain or a loss. For example, the gene gets longer or shorter, it will not detect that.

And there are instances of genetic conditions where the gene length is important in causing symptoms.

It will not detect if there are chromosomes that have stuck to each other and in the process affected a single gene where they reattached, because if there's no net gain or loss of genetic material, you will not be able to detect it. And we know that there's a significant infrequency of these events that can lead to symptoms.

And of course, it will not detect single letter changes in its gene or in the instructions of this gene because it's designed to just look at addresses and not really at reading the instructions within this gene.

Now, we know that the other testing that we typically perform as part of first-year testing is fragile X syndrome testing. We know that's due to an expansion in the size of the letters of the gene FMR-1. And we know that when that occurs, you can have a specific behavioral profile with some physical features that are associated with it.

There's actually carrier screening, meaning this expansion typically happens when the genetic change is passed down from the parents to the next generation. And you can actually identify a pre-expansion that can then lead to the significant increase in the number of repeat symptoms.

And in fact, now many parents during the pregnancy are offered carrier screening for Fragile X Syndrome as part of their pregnancy planning.

Now, chromosomal microarray and fragile X testing was the main paradigm for initial testing offered to individuals with neurodevelopmental concerns, including autism. But this paradigm shifted in 2009, when there were a couple of papers that first described the use of a new technology called -- sequencing to define the cause for rare conditions that escaped and alluded an answer for many decades. And the reason was that this test could actually then in one sample essentially do a spell check on all 21,000 genes, and then identify by using parents as reference where the changes were that were rare enough that could lead to this kind of a presentation.

And of course, by looking at patients that had very similar symptoms, that increased your likelihood that you would be able to find an answer.

So why is it useful? It turns out that, fast forward to a decade later, and many studies have gone

on to demonstrate that there's a high contribution of what are called de novo genetic variants to the predisposition of neurodevelopmental concerns. And in this case, what we're looking at is if you have, again, the genes in both participants, as the genetic material is being passed down, there can be a spell change, a spelling change in one of those many 21,000 genes, that then gets passed down to the next generation and causes neurodevelopmental symptoms.

So this initially research tool transitioned to the clinical realm around 2012, and that ended up being what is now currently known as clinical exome sequencing, a clinical test through many commercial and academic laboratories.

And it's intended to identify about sequence variants or changes in about 95% of all the genes that make protein. It sequences mitochondrial DNA, and that is separate or distinct from the DNA that we all carry in our cells in the nuclei.

It can detect just like the microarray does in many instances the laws of one or more genes in one or two copies of the chromosome. It costs thousands of dollars. It has a 30-day turnaround time. And it requires consenting prior to sending. And that typically is performed by a genetic counselor.

So, as part of this counseling, what we want to obtain is a comprehensive family history as well as past medical records to ensure that we have as much information as possible of what the clinical presentation of the patient, to make sense of what the genetic variants that we identify.

There's a consent process, and it's intended to make families aware, particularly the participant that's getting -- or the individual that's getting the testing, of a number of risks that include identifying misattributed paternity, consanguinity, and change of findings, for which there are opportunities for preventions later on in life.

We take time explaining the mode of inheritance so it's clear what are the potential outcomes of the testing, what the recurrence risk could be once the results are back, your reproductive options, whether this will impact them if that is the context in which it is being performed, and of course, addressing psychosocial issues that may impact the process of testing, which include not only repercussions in terms of family impact, but also financial impact, in terms of insurability.

And of course, we provide community and professional resources that are meant to provide contented counseling at a level that's adequate to each individual family's education level.

So, clinical exome sequencing is ideal in settings where there's a typical history of years without a diagnosis, with a lot of clinically unexpected findings and no one can put the pieces together. Many times, the reason that all of these unrelated and unexpected clinical symptoms being related is because there's a gene that is known to predisposed to all of them, or genetic change.

Of course, we're looking at primarily conditions in which the symptoms don't really tell you which gene is the cause. And there are many so-called genetically heterogenous, meaning symptoms can

be caused bay different number of genes. Some of them include seizures. Seizures can be caused by genetic changes in many different types of genes. Autism is another one. There are also neurodegenerative diseases, as well as diseases of the eye, where you can have the same symptom which is loss of cells in the eye for vision, but that could be due to a number of different genetic causes.

So in those types of situations, doing a test that includes all those genetic causes in one test is much more effective, both cost and time effective in terms of trying to find an answer.

And of course, when you have an atypical presentation of established genetic syndromes, you would never suspect that. So, for example, you might have situations in which you have mostly behavioral concerns, and no other specific neurodevelopmental diagnosis, and a lot of developmental pediatricians and geneticists, we all struggle with the finding of the symptoms are.

But sometimes that is due to sort of, we can call it either mild or atypical presentation of a very well-established genetic condition. And that is one of the questions that I'll pose at the end. But we still don't understand, why is it that one individual with changes in one gene can present so differently, or with a more limited number of symptoms, as opposed to others who develop a pretty much laundry list of concerns.

So, when we discuss exome sequencing, specifically how effective has it been in identifying etiologies of single gene predispositions to autism, we know already, again, from our vast literature, that there's an increased chance of a dominant de novo mutation in autism. We know that having one copy of the two that we inherit in this change is sufficient to give you symptoms.

And de novo, we mean that they happen typically spontaneously, either in the germ line or after conception.

But exome sequencing is identified in de novo mutations in about 50% of autism cases. Sometimes it's associated with advanced paternal age, and we've known from genetic literature for a long time that in certain scenarios, the older the father is, the higher the likelihood is that we've seen of some of these genetic de novo dominant mutations occurring.

Of course, genes associated in addition to with autism with seizures, with ADHD, with schizophrenia, psychiatric disease, and that spectrum of clinical manifestation is part of the question that we still don't understand well.

So the approach to clinical genetic testing to summarize, essentially starts with the clinical diagnosis of a neurodevelopmental concern. Then you decide if it's primarily autism, idiopathic, or isolated, or is it autism with other symptoms. You pursue fragile X testing. If you have a diagnosis, you stop. That happens about a quarter of the time.

But sometimes what happens is you don't get a diagnosis after the first year of testing, so then you move on to the next tier, which could include some sequencing of the second tier, or even as a first tier

test. And I'll give you examples where recent guidelines suggest that.

And of course, if you identify genetic change, which can happen about 30% of the time, then you'll have a potential genetic predisposition identified.

So what happens with genetic testing, and this tiered process or approach doesn't identify a clinically significant brand? What do you do next? What are your options? We get this a lot of the time where we've gone through this journey of trying to find a genetic contribution, and we are coming up empty handed.

I'll give you an example where it's important to follow patients clinically over time, because there's a role for this involving phenotype, meaning how are symptoms changing over time, and how that will impact our ability to understand the genetics of the clinical presentation.

So I'll give an example of the family where the first individual was a child that is 2, who initially presented with just autism, and primarily presenting with pure social cues, differences in eye contact and behaviors, and of course, abnormalities in sleep.

And initial testing that had included clinical exome sequencing revealed no clinically significant variants that could fit his symptoms at the time. But by the age of 4, in addition to persistent autism symptoms, the individual went on to develop progressive regression milestones, significant developmental delay, and volume loss of the occipital region.

So we went back and looked at the exact same genetic information that we had two years earlier, but that we had interpreted with a different set of information in terms of symptoms, and none of these new symptoms had revealed themselves, manifested over time.

We were then now able to find what genetic change is, but we couldn't make sense of, because most of the symptoms were not present, to then lead to a different diagnosis. In this case, a deficiency, which is a progressive and neuro-deteriorating condition that is genetically encoded.

As you can see, due to mutations in an SUMF-1.

We went on to test additional siblings, and we found out that many of the other siblings also were affected with a similar condition, and gone on to develop a similar progression.

But again, this was an opportunity to understand or to reemphasize how the involving symptoms over time are important in order to understand the genetic contributions that we're looking at.

So this is what we call exome reanalysis. It's the idea that because symptoms may change over time, and especially symptoms that we're not expecting, like for example, loss of milestones, that that evolving phenotype may be a clue that the genetic ideology should be looked at in more thoughtful ways, based on those newer pieces of evidence.

And the other possibility is that it may not be that the phenotype or the symptoms are changing, but that there are new genes identified all the time, and the reason no answer is clear at the time of clinical

testing is because the gene is not known at that time to predispose to neurodevelopmental concerns, and that may emerge or evolve as time goes on.

So, of course, over time, more knowledge will be available, more impact the testing can have. And we do know that reanalysis increases diagnostic yield. So one of the largest exome sequencing studies performed in the UK, the deciphering neurodevelopmental study, provided -- through exome sequencing in individuals that have severe developmental concerns.

And when they went back and reanalyzed the data for newly discovered disassociated genes, the yield increased up to 40%. So, again, detailing or proving how the emerging knowledge over time, both from the patient's symptoms and about our knowledge of genetic contribution to developmental concerns, will add to the likelihood of finding a potential for disposition in genes.

So I've told you essentially where we stand in terms of our knowledge of the genetic contributions, at least the rare monogenic ones, to the predisposition to neurodevelopmental concerns. What is left to know?

Well, there are several gaps in knowledge that we still struggle with to this day that primarily are in questions that parents even ask us before we even do the testing, and that is, what is the diagnostic utility of genetic testing?

So once you find a diagnosis, what is it that I'm going to get out of it? How does it change the care that I'm receiving? What is the clinical you till Iowa that have test? And what does the genetic testing cost? And is it cost effective? Does it really in some way impact the care that you are receiving?

That has been a long-standing gap until very recently, where there have been a couple of guidelines out of the American college of genetics and other studies that have gone back and looked carefully through meta analysis, how effective is this approach to testing and identifying diagnoses in individuals with neurodevelopmental concerns.

But also to understand how does it impact care? So this is one of those examples, a meta analysis, a company with a consensus statement, that looked at patients or individuals with neurodevelopmental conditions who are producing a higher molecular yield in terms of diagnosis, of 36%, than just doing chromosomal microarray testing alone.

So just that kind of confirmed our own internal data and that of others, in suggesting how significant the increased diagnostic yield can be using or implementing exome sequencing.

Now, when you sort of look at isolated neurodevelopmental concerns with no other medical concerns, the yield is still around 31%. And when you increase or you add out of those cases the ones that have more clinical concerns than just their neurodevelopmental presentation, the yield goes up to 53%.

So, again, in situations where you have a complex medical history in addition to

neurodevelopmental concern, the yield of exome sequencing is even higher than when you just look at the neurodevelopmental concern in isolation.

Now, if you break that down into different categories, so for example, if it's primarily intellectual disability, the yield is as high as 39%. If you focus primarily on autism, the yield is much lower, it's 16%. But if you look at the mix or a combination of autism with intellectual disability or delays, the yield then remains about 39%.

Of course, if you look at families and relatedness, that yield will be fairly high.

So that has led to try to implement exome sequencing as a first-year test that can then lead to additional inclusion if there's no analysis involved, meaning sometimes exome sequencing, as I mentioned earlier, can tell you if there are neighborhoods of genes that are missing, if that is not available in the clinical test that is being offered to the patient, you can add copy number variation as a tool to then eliminate that possibility.

So we have now enough evidence as part of this meta analysis that looked at studies between 2013 and 2018, to then comfortably propose that exome sequencing that would potentially be a first-year test as a diagnostic test.

Now, it turns out that if you look at the management, post-diagnosis, what happens once the diagnosis is achieved? It turns out that among those that are diagnosed by exome sequencing with a genetic condition, there were changes in medical management about 30% of cases. And there was an impact or reproductive planning of about 80%.

Now, what exactly are those management differences? If you look at another large study, they looked at a significant number of cases, they span between reproductive planning, disease monitoring initiation, investigation of involvement of the disorder with other organs being affected, alterations of the presumed pattern, whether that's been clarified.

Changing of prognosis, where the outcome of the diagnosis is that we know a better sense of what to expect down the road. Changes in medication. And of course, participation in clinical trials.

Now, when we look at that subset of individuals where there's a high yield of genetic testing diagnoses, and the core symptoms, this is a graph from another study that looked at what is the incidents or the frequency of intellectual disability and autism, or either one of them together. In individuals that have a specific known etiology that predisposes to autism. It's all over the place.

In most cases, most of the individuals present with some kind of degree of developmental disability or intellectual disability. There's a small subject of genetic etiologies that have some ASD cases, where the ASD symptoms are the only clinical presentation. But you can see that there's also a significant overlap of both autism and ID in a large number of them.

So that also has made it very clear to us that the spectrum of findings in individuals with autism

increases yield, because a lot of these genes are also involved in predisposition to intellectual disability, and therefore, it makes sense that that will sort of enhance our ability to find a genetic etiology.

Now, in addition to neurodevelopmental concerns, like intellectual disability, we also like at microcephaly, seizures, low muscle tone, dystonia, other clues that might enhance the likelihood that there's a genetic predisposition.

Now, what is the impact on outcomes? What ends up happening over time? Well, there's actually another clinical guideline that was recently published by the American College of Medical Genetics, which is a practice guideline, where it suggests having done an evidence-based analysis that exome and genome sequencing should be available for individuals with intellectual disability and congenital abnormalities.

It comes short of recommending it for individuals with autism, with or without congenital malformations, because they thought it was out of the scope for their guideline. But it does appear that having a diagnostic yield of 38%, which is what this independent but similarly equally powered metaanalysis of the previously available outcomes data in terms of diagnosis, confirms again that the yield is between 35-38%, and that again, compared to a yield of standard genetic testing of 21%. And of course, when you use genome sequencing, which actually sequences every single part of, not just that that makes protein, the yield is even higher, about 43% compared to exome sequencing alone.

So what is the impact on clinical outcomes? It turns out that is part of this meta analysis. They found that as about 8% of individuals, it actually had an impact on the rate of short-term clinical management. It had an impact in long-term clinical management as well in 10%. It had an impact on reproductive focus outcomes as well as family outcomes as well.

So clearly exome and genome sequencing is having an impact on clinical care, and it's perhaps not that different from other modalities that are implemented as part of surveillance screening in the population for making recommendations about additional clinical management changes.

But the remaining question is all the costs associated with it and the barriers to having access to it. We know it can run in the thousands of dollars, the cost of this approach. And particularly, when you start with exome sequencing, which can have a very high sticker price, depending on which institution or which laboratory you are affiliated with.

And of course, if there are additional clinical situations, other diagnostic approaches that need to be done, that it further enhances or increases the cost.

We know that the impact of genetic testing is significant, particularly in the newborn setting, and this is something that is emerging recently. And I'm not going to spend a lot of time discussing it, but it's this idea of doing genetic sequencing soon after birth or perhaps even including prenatally. And the idea would be to screen for a lot of these conditions.

And it turns out when you use this kind of testing, at least in the intensive care unit setting, you actually get a shortened diagnostic journey, where you have a diagnosis within a reasonable amount of time after birth.

And it can actually alter clinical care in about 72% of cases. So it can have a significant impact in certain settings, and the question will be, can that be translated into more modest, but equally important impacts in clinical care outside of those intensive care units.

So where are we going next? What's coming down the horizon that we're going to hear about soon?

So we've spoken about the diagnostic journey, which I've called the diagnostic odyssey, because it's quite a harrowing journey that many both individuals and families go through that includes the genetic evaluation, the initial diagnosis by a specialist or primary physician, that then brings together both clinical and research genetic testing to bear.

With the intent of finding a diagnosis, we always envision that as being sort of an open door for an opportunity to end this diagnostic journey and odyssey.

But essentially what we see is, rather than doors, we see a funnel, and the funnel is part of the odyssey and the challenge that we see. And that's because this genetic testing, as it gets more cutting edge, and it becomes more comprehensive, it becomes harder to justify its medical utility, and therefore, it usually goes through a period of time where studies have to be implemented, that demonstrate its utility, both in the clinical setting and in general outcomes for individuals before it actually becomes standard of care that is covered by most insurance companies.

So we know that things that have been around for a long time are easier to get covered and are more represented by most insurance plans, but as we get to single gene panels, single gene testing, multiple gene testing, and exome sequencing, that that funnel gets tighter and tighter.

So we want to develop or evolve a paradigm where we kind of flip this pyramid down, and try to see if we can get more access to these modalities of testing as soon as possible, to as many people as possible. And that comes along with racial disparities in terms of access to care.

So, what we want to do is to facilitate this process of turning the diagnostic journey or odyssey into a post-testing surveillance and discovery journey, or PTSD, which is what happens after you have that diagnosis. So we've already discussed that it has an impact on clinical care and outcomes, and that happens through multi-disciplinary clinics, depending on the genetic diagnosis or disease-specific clinics. And of course, interacting with care for family planning.

But of course, that also opens the opportunity, once you have a diagnosis, to belong to a community of support groups where you have access to social media, to groups of individuals and families that can help with your journey post-diagnosis. It serves as an opportunity for advocacy for

that particular genetic cause.

And of course, the opportunity to develop foundations and infrastructures that will support the research and the care for -- access to patient care for those particular causes.

And of course, it also opens the opportunity for research, because at that point, you can then develop registries that can capture the natural history of what happens to patients over time, which I told you is very important in both the diagnosis, but also in the post-diagnosis journey.

The opportunity for therapies, in this case being developed. But also, the opportunity to understand what are interventions that can improve the health of patients that have been diagnosed with these rare conditions.

And of course, all of that is dependent on diagnosis, and bridging that gap in access to that diagnostic tool is part of what we would like to emphasize.

That leaves about 44% of individuals where we still don't know what the genetic contribution is. And the next step or tool that's available to break down that barrier is whole genome sequencing that is being paired with a number of other genome technologies that, for example, we're only looking at DNA sequence, but also looking at the RNA sequence, which is the message that the gene sends to the cell and the body to make proteins.

But also look at the modifications that happen to genes, which we call epigenetics. Each one of those levels of regulation of gene expression may have an impact in our understanding of how neurodevelopmental symptoms, including those of autism manifest.

Particularly, if you couple that, with for example, understanding how our body metabolizes substances.

So whole gene RNA sequencing is being implemented as part of studies that are trying to understand the diversity of genomic testing in neurodevelopmental changes, including autism. And we already have a snippet or a glance at that data, and it looks like it does have a significant yield in finding de novo changes, as well as in trying to couple this information with, when you don't find changes that are associated with a single gene, can we then use the variation in genetic changes that are more common or prevalent to develop what we call assessment of combinations of genetic variants that increase your risk, and how predictive that is of you developing neurodevelopmental symptoms.

Of course, that's being coupled with RNA sequencing. We're understanding the diversity of how genes are expressed and spliced together early during development, but also after birth is going to be important in understanding how that can lead to some of these.

This is an example, again, of one of those large studies that has looked at a whole genome sequencing in patients with rare diseases in the setting of a national health system. And again, about 16% of those individuals, independent of the diagnosis, whether it's neurodevelopmental or not,

received a diagnosis.

So proving that even at a population level, it can actually enhance the ability to reach a diagnosis, when implemented as part of a health system enterprise.

Now, one of the questions that has emerged from those studies and the question that is still remaining is why is it that some individuals that have either identical or similar genetic variants, why do they either never develop them or why do they develop some of those symptoms and not all.

And we feel that that heterogeneity can be important in understanding the contribution from some individuals and why many individuals may sort of skirt through and not get testing, because there's not enough clinical presentation there to warrant the testing.

But where the testing could have had an impact, had it been done in a timely manner. So we're trying to figure out how to put those pieces together, and that information will come down the road as more sequencing and data is available.

We also know that parents with a strong family history of neurodevelopmental and psychiatric conditions can have a higher, what we call variant burden or changes in the genetic material that in combination may sort of increase the likelihood.

And in fact, there are studies that have found that you can have rare genetic changes that in association with genes inherited from the parents' background can also modify or change the way that those symptoms manifest. So, again, taking into account the background of genetic changes in the setting of the family history, it's also going to be important to understand where a single rare genetic condition is not identified.

Of course, there's also mechanisms of genetic differences that could present that may be limited, because you have to actually sample or obtain a tissue that is affected in order to find or identify the genetic cause.

And that happens in situation that we call mosaicism. As you can see here, in most cases, the genetic change that we inherent in our body is distributed throughout the whole -- all of the cells of the early fetus. But sometimes it's only present in some parts of the fetus and not all of them.

And there are symptoms external physical manifestations that can suggest that change. For example, pigmentary changes like the one here, where you see there might be a genetic change in the left pigment of the region. That can happen in the brain specifically, where we know a lot of these genetic changes are found only in the brain but not in other part os. The body from some of these studies.

And it may account also for why we see individuals that present with not all of the classical symptoms at one specific genetic diagnosis.

We need to update natural history studies of these conditions when they're associated with autism

or intellectual disability to see how they respond to interventions and how communication tools will help identify language disorders within intellectual disability.

We need to know how much more will genome and maybe the epigenome sequencing will add to our diagnostic yield and genetic testing. We need to provide multi-disciplinary care to families that have reached a diagnosis to anticipate comorbidities and interventions and to power or leverage through all our registries to identify what is it that we need to look for.

And of course, design clinical trials in those situations in which there may be a therapeutic intervention to implement.

So, as part of the genetics node, we have several priorities. I won't go into detail into all of them. But essentially what we're trying to do is to try to facilitate research that fills gaps in knowledge on the benefits of genetic testing, the setting of the medical care for individuals with autism and to understand better how it's clinically useful.

Also, reduce barriers that lead to long diagnostic journeys for individuals with concerns. And of course, to enhance our understanding of the natural history for many of these rare monogenic causes, to leverage that for opportunities to improve care, but also to perhaps identify therapeutic interventions.

So with that, I would like to thank the AIR-P for their help in giving me this platform, to share this information with you. And, I'll leave it to Maddie to take it from here.

>> MADELINE HALEY: Thank you so much, Dr. Martinez. So, I think now we have some time for questions. It doesn't look like we have anything in the chat right now, but I know that was a super interesting topic, and it was a great presentation.

I'll give it just a couple minutes for any questions to come in.

In the chat, someone said, is there a difference between whole exome sequencing and clinical exome sequencing?

>> DR. MARTINEZ: So, it's actually a very good question. So, whole exome sequencing was a term that was originally used to identify or tried to describe that every single gene was being sampled or assessed for changes or differences.

What we've known over time is that the technique that's used is not 100%, so using the term "whole" was a little bit misleading. Now we use exome sequencing as a substitute, because it really describes what its intention is. It's in the clinical setting to try to assess as much as possible any differences in exomes, but knowing that there's some limitation.

It does not cover everything. It covers about 95% of what those sequences should be.

>> MADELINE HALEY: All right. And then some very wonderful feedback. The term diversabilities, I agree, that's a super cool term that we should definitely start incorporating more in our network.

Somebody asked, can you explain more about the clinical implications. So, like what difference would a genetic diagnosis mean?

>> DR. MARTINEZ: Right. We went through some of those examples, but I'll dig a little bit deeper through some of them. One potential outcome could be where identifying a particular diagnosis then leads to a known genetic condition in which we anticipate, for example, seizures happening down the road.

And then that individual undergoes an evaluation for it. You identify differences in sort of brain activity, and that allows you as an opportunity to identify interventions that can prevent them, or if they start happening, proceed with taking care of them.

There's a situation in which why this diagnosis could be benign tumors or tumors that could develop into cancers, so that would be another situation in which implementing surveillance could be helpful.

And there's a very small subset in which we know there are interventions there are therapies that can actually be helpful in allowing the individual to improve their clinical health. And, for example, it could be the predisposition in a genetic condition to immunodeficiency, and having had a history of multiple infections, being able to implement treatments that will reduce the likelihood of those infections and their consequences.

So that's a clear example where it can have an impact on medical care.

Now, there also may be impacts on family. So we know that when we have more than one affected child in a family, that having one affected sibling and have genetic testing done, many times they share the same genetic etiology. So that can then open the door for discussions about family planning.

But also about discussing heritability. In many cases, we found that genetic cases are inherited from a family member, maybe one of the parents, and it wasn't clear that there was a predisposition there, but that serves as an opportunity for self-discovery and more insight on the part of the family member to then discuss, well, if I look at my past medical and behavioral and health history, do I see differences there that actually now give me some insight as well.

And of course, that also has implications for other family members. Nieces, nephews, other parts of the family could be affected. For reproductive status and also for self-discovery in terms of understanding whether they've had their own journeys, but that wasn't very clear to them.

Finally, I think there are opportunities for improving the amount of therapies that are actually developing. So, for example, there could be an opportunity for a gene that there isn't much known about right now, but through research and through registries and through gathering understanding, oh, there are clinical concerns or complications we weren't aware of, that by bringing that information

together, it will help us understand what to anticipate and screen for.

But also an opportunity for contributing to research that may be part of clinical trials that will then lead to interventions in the future, whether they are medications or sort of this emerging field of gene therapies, which is now becoming part of the standard of care for our neurodevelopmental colleagues. And neurologists.

So hopefully that gives you sort of a breadth of spectrum of where it can have an impact.

>> MADELINE HALEY: Thank you, Julian.

One more question I see in the chat. In siblings, have you seen the differences in male versus female. This person said that their son and daughter present very differently.

>> DR. MARTINEZ: Yeah. I mean, I think that's a very good point. There is this phenomenon that is well-known in the neurodevelopmental literature where there can be differences in how -- behaviorally, the behavioral profiles of males versus females when they present, including autism. I think it depends on timing and how those differences manifest.

And that can sometimes lead to delayed diagnosis, because many times, depending on whether you're a male or female, that would be recognized more significantly than -- or maybe more impactful than others.

And in fact, there's also this process of masking where there's a lot of opportunities, where depending on whether you're male or female, you might have more ability to be able to sort of screen under the radar for some of the assessments, bypass or not score to an extent that it will be diagnostic.

Now, when you transition that phenomenon to genetics, there actually are genetic conditions in which we know that males are more affected than females. Fragile X Syndrome is one of them. That has to do with the fact that there are genes that are primarily present on the X chromosome, for which boys only have one. And that can definitely lead to differences, whether it's a boy or a girl or a female or a male.

And in the same situation, there are specific genetic causes where we know that only females are affected and not males. So there's a spectrum for those differences, and we know that, yes, the chromosomal complement in terms of X and Y, can sometimes can actually manifest differently, depending on the presence of those chromosomes may affect the manifestation of the symptoms.

>> MADELINE HALEY: Thank you. All right. I think we have time for maybe one or two more questions, if anybody wants to ask a couple more.

I will also take this time to send the link for the feedback survey. So this will -- if you can provide your feedback and also if you have any topics that you would like us to present on in the upcoming months, that would be great.

The other thing is, Julian, if you want to go to the next slide, please. Yes. So, we have a -- we

have our webinar next month in October. And I will send you the Zoom link to register for that as well.

All right. It looks like we don't have any more questions, so, thank you again so much, Dr. Martinez. And everybody, have a great rest of your day, and we'll see you next month. Thank you.

>> DR. MARTINEZ: Thank you, everybody.