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Newborn Gene Sequencing: Expanding Early Detection of Treatable Diseases

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature is titled “Newborn Gene Sequencing: Expanding Early Detection of Treatable Diseases,” featuring Physician-in-Chief, Dr. Jordan Orange; immunologist Dr. Joshua Milner; gastroenterologist Dr. Steven Lobritto, and electrophysiologist Dr. Eric Silver. All pediatric specialists are practicing physicians at Morgan Stanley Children’s Hospital at NewYork-Presbyterian and Columbia. This podcast is a production of NewYork-Presbyterian with world-class doctors from Columbia & Weill Cornell Medicine.

Dr. Orange:
My love for immunology came first. The reason is that I was so captivated by the fact that most people were healthy most of the time. Most people are not in hospitals. Most people are living their lives. And as a young person, I was really captivated by what defines that difference between people who are sick and people who are well. Increasingly, we realize that that is in the genes or has something to do with the genes.

Erin Welsh:
This is Dr. Jordan Orange, Physician-in-Chief at the Children’s Hospital of New York at NewYork-Presbyterian Morgan Stanley Children’s Hospital.

He’s also a co-author of the GUARDIAN study – which stands for Genomic Uniform-screening Against Rare Disease in All Newborns – and was launched at Columbia under his leadership.

Dr. Orange:
The GUARDIAN program was really set up to try and be sure that we're able to apply the learnings of genetics to our newest lives. And to do so in as unbiased a way as possible, to give as many children as possible that best chance in receiving a treatment, receiving a cure before a child has become sick with a condition.

Erin Welsh:
If this sounds familiar, you might have listened to an earlier episode of our show featuring Dr. Wendy Chung. She executed a ground-breaking study mapping newborns’ genomes in order to look for the genetic mutations which cause spinal muscular atrophy – a life-ending diagnosis.

That study has now blossomed into the GUARDIAN program, which began by using genome mapping to look for not one, but 156 rare but treatable genetic conditions. That’s dozens more than the current standard for newborn screenings. And today, that number continues to grow, with screenings for up to 450 conditions.

I’m Erin Welsh and this is Advances in Care, a podcast about groundbreaking developments in modern medicine. In this episode, we’ll hear from four physicians from the Children's Hospital of New York at NewYork-Presbyterian who have contributed to the GUARDIAN program. Their work provides a blueprint for a revolutionary approach to newborn screening. We’ll learn about their interventions thus far, which have already spared families the heartache of learning about genetic diseases before it’s too late.

Dr. Orange:
Presently, all states in the United States have a newborn screening. Depending upon what state you are in, there are between 30 some-odd and 80 conditions that are screened for.

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But between 30 and 80 is really just a subset of diseases that can be diagnosed early in life. And we increasingly know that the answer to many of these conditions is held in the genes and the diagnosis can be made immediately because of the genetic information.

Erin Welsh:
The standard heel prick test is always offered to newborns and their parents. At the outset, the ambition behind GUARDIAN was to provide that same level of accessibility, but to a much more thorough and technologically advanced screen. So that all families could get critical information about their child's health and make life-saving diagnoses. But to do so would be a goliath task.

Dr. Orange:
This was not novel or unique, but what was, was assembling it and doing it. To be able to have the partnership with New York State, to be able to have an institution that was open to this being part of care. And so it really required a large scale initiative to be able to bring this genomic technology potentially to every new life within our system.

Erin Welsh:
To be successful, Guardian needed geneticists to find gene mutations which link to disease, advisors to enroll parents in the trial, labs to analyze the samples, genetic counselors to work with families who get a positive result, and a pipeline to the physicians who can actually treat the patients. And on top of all that, they'd need to enroll a lot of babies.

Dr. Orange:
The initial goal was a bold one to try and screen 100,000 newborns. And the reason for choosing 100,000 is we know that there are some conditions that are so rare that are included in GUARDIAN screening that we would probably need to screen 100,000 newborns to find some of these conditions. But the longest journey starts with a single step, and we had to get going, and we had to start one newborn at a time.

Erin Welsh:
So, they started small with 5,000 newborn babies born in New York City. And the location here matters – because in order for a study like this to be successful, it's really important that the participants are racially diverse. A homogenous population would massively limit potential findings about genetic disease. Luckily, NewYork-Presbyterian and Columbia serve extremely diverse patient populations. But one big question remained: [00:05:00] would they actually want to participate?

Dr. Orange:
In our hospital system, we care for many who associate with historically marginalized populations and communities. And we know that trust for research faces its challenges.

Erin Welsh:
Based on historic examples of discrimination and exploitation in medical research – like the Tuskegee Syphilis Study, for example – Dr. Orange and his colleagues knew that it would be important to establish trust. And that getting these communities involved would be a huge win in rebuilding that trust.

Dr. Orange:
One outcome that we were very worried about, was that those associated with historically marginalized communities would choose not to participate in GUARDIAN. Fortunately, that did not happen. We had tremendous participation diversely across the communities we serve.

Erin Welsh:
So, GUARDIAN began screening a large, diverse population for genetic conditions that might be missed by a typical newborn screen. And before long, they started getting positive results...

Dr. Milner:
One of the genes that we screen for is IL-2 RG. The IL-2 receptor, which is also referred to as X SCID or X Link SCID.

Erin Welsh:
This is Dr. Joshua Milner. He's an immunologist and co-author of the GUARDIAN study. He's talking about the genetic mutations which cause SCID – or Severe Combined Immunodeficiency, also known as "bubble boy syndrome." Babies born with SCID lack the ability to make working T cells, so they're extremely susceptible to infection. Many die within the first year of life. Luckily, all states in the U.S. offer a screen called TREC – or T cell receptor excision circle – on newborn babies. But it can't catch all forms of SCID.

Dr. Milner:
It only affects boys. It should be caught using the regular newborn screen because you just don't have adequate T cells being produced.

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However, in recent years, we've been able to identify that there are people who have mutations which do not as severely affect the IL-2 receptor. And in those cases, when it's milder, the numbers of the T cells are adequate so that they don't screen positive in the regular newborn screen.

Erin Welsh:
When the disease manifests like that, it's called "atypical SCID." And it's extremely rare. But it's just as critical to intervene early as you would with any other case of SCID – with a bone marrow transplant.

Dr. Milner:
Doing that bone marrow transplant within the first three months of life and before an infection happened leads to a 90 plus percent lifetime cure rate which is incredible.

Erin Welsh:
But of course, if a baby has SCID, they often won't be diagnosed until a major infection happens, and then – it's often too late to intervene and save them.

So, when the GUARDIAN screen caught that IL-2 receptor mutation in a baby who'd had a normal TREC test – testing negative for any type of SCID – Dr. Milner knew it was important to act fast.

Dr. Milner:
The genetics folks sent us the result of the screen. They said they have this mutation which really is so incredibly rare that we're just not sure that it causes disease, but there's enough of a reason to follow up. There's always sort of another test that you do to verify the problem, and with severe combined immune deficiency, that's usually we just do something called flow cytometry, where we send a blood sample to the lab and they just literally count the T-cells a different way. But that also was normal in our patient, which is what can happen when you have these milder mutations.

Erin Welsh:
But because he had confirmation of the mutation from GUARDIAN, Dr. Milner kept pushing. He called for yet another test to check the function of a protein in the patient's sample.

Dr. Milner:
And that showed a gross abnormality that essentially proved that this is indeed what's happening in this child. And that he is at extraordinarily high risk for life threatening infections, but maybe not in the first year of life. It might be later.

When this result came back on this child, it was very clear we need to make the decision to do the transplant now, even though it may be a whole year before an infection happens, because this is the safest time with the best outcome.

Erin Welsh:
Of course, a bone marrow transplant is a complicated and painstaking procedure.

And telling a parent that their newborn baby will have to undergo it isn't easy news to deliver. Especially because right at birth, babies with SCID look perfectly normal.

Dr. Milner:
You know, it's a little bit shocking. Like, "Oh my gosh, my beautiful looking baby. What are you saying?" Not only that, we're going to do a pretty major intervention to save this perfectly good looking baby's life. And we've got to do it now before we even see the baby getting sick. I think that can always be jarring. Another way that sometimes we'll know that a baby might have SCID is that there is somebody else in the family who has SCID, but here this was absolutely out of the blue.

I think what was remarkable was the mom was like, "Fix it and fix it now." This, to our knowledge, was the very first time this has ever happened. That a genetic newborn screen was able to identify a treatable immune disorder when the regular screen couldn't pick it up and where it wasn't running in the family. That's the first time that's ever, ever, ever happened. It was very, very exciting to us because it also just immediately validated that you have to do this.

Erin Welsh:
What was also remarkable was simply the fact that GUARDIAN caught a case of atypical SCID within the first 5,000 babies screened.

This is a disease with an occurrence of 1 in 50,000.

Dr. Milner:
We sure as heck didn't expect to get called at all in the first year, or the second year, or the third year, because they were only supposed

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to do about 50 or 60,000, babies, and if they're only screening for severe combined immune deficiency genes, it was gonna be 1 in 50,000, right? So we were kind of shocked that only a few thousand children in, we already had a positive hit.

Erin Welsh:
It was like being struck by lightning. And then… Dr. Milner got struck by lightning again. GUARDIAN diagnosed a second case of atypical SCID.

Dr. Milner:
This is still with fewer than 10,000 babies screened. So we're talking about two leaky severe combined immune deficiencies out of 10,000. Now this is no longer an accident. This is telling us that even just that one type of immune problem, you know, somewhere around one in 5,000, that's really incredible that that could be the rate that that's happening. And we wouldn't have known it any other way.

Erin Welsh:
The GUARDIAN screen eventually expanded to look for other genetic issues related to severe but treatable immune disorders, like SCN or severe combined neutropenia, which is a deficiency in white blood cells called neutrophils.

There are many patients with genetic diseases which are caused by mutations that haven't yet been identified in the genome. But Dr. Milner emphasizes that the GUARDIAN program can still potentially help those people in the future.

Dr. Milner:
We are able to reanalyze the genome sequence at any point in time. So we may be able to discover new genetic causes, for instance, of a new immune disorder, when a child has an issue that they come into the doctor for, and we're able to quickly reanalyze that on a research basis. So that the next child who has that same genetic problem, we know what it is and what it's causing. And it ends up on that very long list of genetic problems we screen for. So it's actually new disease discovery and new cure discovery that can come from a program like this.

Erin Welsh:
While SCID is a serious disease that requires extreme and immediate intervention, GUARDIAN also screens for genes linked to illnesses that, if managed properly, don't always become serious. That is – if the patient knows about them early in life. Take, for example, Wilson's disease.

Here's pediatric gastroenterologist Dr. Steven Lobritto.

Dr. Lobritto:
The genes for Wilson's disease are known. One of the genes sought after was the Wilson's gene. It's known as the ATP7B gene, and it is on chromosome number 13. Knowing that the patient has a pathologic gene, since it's an autosomal recessive disorder, allows us to focus on these patients before they develop disease in the future.

Erin Welsh:
Wilson's disease causes copper to build up in the body, and it causes organ damage to the liver, the eyes, and also the brain. But it's not screened for in newborn blood tests. And you can't really diagnose it in babies because there hasn't been time for copper build-up.

Dr. Lobritto:
The usual presentation for Wilson's disease will be a teenager with the abnormal liver test. By that time, there's significant liver injury. Or they present with acute liver failure and need an immediate transplant to survive.

Erin Welsh:
But here's the thing: If Wilson's is diagnosed early… The treatment is extremely simple.

Dr. Lobritto:
You could actually prevent copper from being absorbed by giving zinc, a simple mineral that competes with copper absorption.

Erin Welsh:
That's right. Just a regular dose of zinc can prevent the need for a liver transplant. There are also dietary guidelines a Wilson's patient can follow, basically avoiding high copper foods like legumes and chocolate.

Dr. Lobritto:
There's a lot of benefit to knowing someone has this upfront, even though at this very moment in time within that first year or so of life, I really don't need to do anything to intervene other than to identify these patients and possibly give them some dietary counseling to prevent a rapid accumulation.

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Erin Welsh:
But of course, avoiding organ damage is only possible if Wilson's patients are diagnosed before they show symptoms of copper overload. And that's what genetic sequencing allows for – knowledge of those genes, and then the opportunity to prepare families for those lifestyle changes and possible interventions later in life. Here's how Dr. Lobritto helps those families move forward.

Dr. Lobritto:
These patients are being sent to me at two, three months of age, right? They have been identified as having abnormal genes. So the first part is to explain to the patients to interpret what I think is the actual risk of Wilson's given some of the genes are pathologic and others are not.

Erin Welsh:
Granted, Wilson's is a rare disease, only prevalent in 1 in 30,000 individuals. But GUARDIAN already flagged a handful of babies with associated genes.

Dr. Lobritto:
They've identified four children within the Columbia system that carry genes. Some are definite and a couple are, one definite gene abnormal and the other one just not known. And that's one of the limitations of genetic screening is that even if you identify a novel gene, you don't know if that gene is going to cause disease. Now certainly following the patient over time, you'll find that out, and then that gene will become a known gene as opposed to an unknown gene. So every time we do genetic sequencing, our genetic database gets smarter.

Erin Welsh:
It's also a huge relief for families to have that knowledge about their new baby as they prepare for the future.

Dr. Lobritto:
They leave the office with some knowledge, right. An understanding that we still have work to do as far as even confirming the diagnosis [00:16:00] and that there is no urgency at this stage, though it is important to follow through so that we prevent the need for any urgent intervention in the future. I think it goes a long way.

Erin Welsh:
Wilson's often runs in families, so identifying a gene in a new baby can also help flag potential for the disease in siblings. And it's not the only condition GUARDIAN screens for that can make a difference for family members, too. Long QT syndrome is a heart rhythm disorder. It can be acquired through certain medications or other medical conditions, but it can also be inherited. Here's pediatric electrophysiologist Dr. Eric Silver.

Dr. Silver:
Long QT syndrome is a disease where you can see an abnormality on the EKG and it goes along with a risk of having abnormal rhythms that potentially could be very dangerous. Patients can have episodes of fainting or can die suddenly related to these abnormal rhythms.

Erin Welsh:
But it's difficult to pin down in infants because infants don't get EKGs. It's also not a condition included in regular newborn screening.

Dr. Silver:
There are various genes that cause long QT syndrome. The ones in the GUARDIAN study are the most common ones of those. The primary one is something called KCNQ1. That's long QT syndrome type one. It's the most common type of long QT syndrome.

There is a risk of arrhythmias from the time of birth. So the fact that we know about it now allows us to put the patient on medication that can significantly minimize the chance of having any arrhythmias going forward.

Erin Welsh:
Treatment is life-saving, but it's fairly straight-forward: a combination of prescribing beta blockers, avoiding certain medications that affect the heart, and advising patients to be cautious about strenuous physical activity.

But the genetics are a little less straight-forward. Geneticists have identified genes that are associated with Long QT, but having a mutation doesn't mean the patient certainly will have the disease. So when the GUARDIAN screen identified a potential case of Long QT, Dr. Silver's first step was to confirm the results through a series of EKGs. On the patient and the patient's family members.

Dr. Silver:
We did not just one EKG, we did serial EKGs. We also did EKGs on other family members like the parents and the father turned out to have the same genetic defect.

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Erin Welsh:
Thanks to GUARDIAN, both the child and father are now on medication to prevent abnormal heart rhythms.

Dr. Silver:
My analogy that I talk to families about is, I think of the genes as like a book. And each of the genes is a chapter in the book. And if you are reading through, there are times where you see a spelling error, but you can read right past it and you understand the meaning of the sentence, even though there was a spelling error. That's happening all the time in our genes, where there's little changes from person to person, but it doesn't reflect any changes in the way their body functions. There are times that there is a change where it totally changes the meaning of the sentence and that's where a disease comes about. And there are times that we just don't really understand how much it might confuse the body. And that's where we're trying to get better.

If we continue to improve and understand these diseases much more specifically where we don't have this level of confusion at times. That's a huge promise for this study in general and genetic testing moving forward.

Erin Welsh:
Of the first 4,000 infants screened by GUARDIAN, 120 tested positive for genes associated with treatable conditions. And 110 of those positives were not detected by regular newborn screening.

Dr. Orange:
Now the results of GUARDIAN were really what were inspiring in that a majority of the diagnoses of these conditions via GUARDIAN occurred in individuals associated with historically marginalized populations. That was really, really meaningful.

Erin Welsh:
Dr. Orange emphasizes that the GUARDIAN study isn't a technological accomplishment. Genetic technology is out there. It's available. He often says, "anyone could have done this." But the truth is, others didn't do it. Because what was really required was the ambition to dream big, to tap into the resources and network of the institution, including the families it cares for. And – the will to transform pediatric care.

Dr. Orange:
The study continues and we have now screened over 10,000. I think we have a lot of ground to cover for something like GUARDIAN to be the new norm. There's certainly a cost to doing genome screening. And we have to get very specific in terms of the number of conditions that will be screened, and the infrastructure more broadly, to be able to deliver on the information that's derived. There's a lot to be sorted out. But I do think that there's a real value proposition to everyone involved by continuing that work and getting to that place.

Erin Welsh:
Dr. Orange and his team at the Children's Hospital of New York at NewYork-Presbyterian Morgan Stanley Children's Hospital continue to rally the resources to expand the project so it can one day be adopted on a broad scale.

He hopes that the results of GUARDIAN will set a new bar for newborn screening across the country.

Dr. Orange:
GUARDIAN is just an example. GUARDIAN is just a use case. It's a demonstration that something can be done. How many GUARDIANs do we need before we change policy? Before we go about things in a different way. How many lives need to be saved? How many diagnostic odysseys need to be eliminated? How many dollars need to be saved by not having somebody that has gone through a series of profound illnesses and hospitalizations? I don't know the answer to that question. But what I do know is that the results from GUARDIAN are there and that they'll keep coming.

Erin Welsh:
Thanks to Dr. Orange, Dr. Milner, Dr. Lobritto and Dr. Silver for taking the time to share their stories about the GUARDIAN program.

I'm Erin Welsh.

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