# **Transcript**

**Clinical Trials for One Patient with Dr. Joe Gleeson**

Stan

Hello. I'm Stan Crooke, and welcome to the n-Lorem podcast series, a podcast series that focuses exclusively on the needs of patients with nano rare diseases. Today, I'm privileged to have as a special guest, Dr. Joseph Gleeson. Joe, welcome.

Joe

Thank you so much. I'm very pleased to be here.

Stan

Dr. Gleeson is the Rady professor of neuroscience and Pediatrics at UCSD in San Diego. He's also the director of neuroscience at the Rady Children's Institute for Genomic Medicine, and in addition to all of his other responsibilities, Dr. Gleeson has joined n-Lorem as our Chief Medical Officer. Dr. Gleeson is a world-renowned geneticist, neurologist, and pediatrician who's been recognized with many awards, including, most recently, the Bernard Sachs Award from the Child Neurology Society, and he is a member of the National Institute of Medicine of the National Academy of Science. So, Joe, again, thanks for joining us.

Joe

I'm really pleased to be here. I feel that we should be trading places because I it's usually the more distinguished person that is being interviewed, so please forgive me.

Stan

Well, we can trade distinguishes over time. So, Joe, I know you're a California lad and you actually went to UCSD as an undergraduate in chemistry. So, do you use chemistry in what you do every day?

Joe

I do actually. Yeah, I really look back on that experience, you know, with fondness. I learned so much from so many people about how to think about how chemicals interact and how chemistry works, and that really framed how I approached medicine, in a way, because I thought about things from a very reductionistic point of view. The body is a series of a number of chemicals that are interacting with each other. And that's also how I think about medicine, you know, and thinking about drugs. Chemistry is a wonderful background for medicine.

Stan

Oh, I couldn't agree more. So, when did you decide that you were interested in medicine as an expression of chemistry?

Joe

Well, I was finishing up college and it was going to go one of two paths, either chemistry or medicine, and I really enjoyed my interactions with patients. I was volunteering a bit at the hospital in San Diego, and I figured this would be a really good way for me to apply what I had learned in college. And I decided if I went that route, what I really wanted to do is figure out how the brain works. And from the point of disease, you know, and that's kind of been my mission. How do we think and feel? How can disease teach us about how the brain functions? And that question has evolved now into how can we cure patients? You know it's really part of the same journey for me.

Stan

Oh yeah, very much so. So, you traveled east for a while. You went to Pritzker Medical School at the University of Chicago. And then you did your residency and fellowship at Harvard. Is that right?

Joe

Correct yeah.

Stan

And so, chemistry to how the brain works, then medicine, but then genetics?

Joe

Yeah, I was really fortunate to have a series of mentors as I went through my training. First at the University of Chicago, a fellow named Peter Huttenlocker, who really opened my eyes to child neurology, which is the study of really how the brain forms and how we mature as humans. And then at Boston Children's Hospital, where I did my pediatric residency in neurology, and it was there I saw so many patients where we had no answers. Every patient was another mystery. We knew of a total of about five diseases. We had Tay Sachs disease, we had spinal muscular atrophy, Down Syndrome, fragile X. And that was it. And every other patient, which was 99% of the patients that we saw, had no diagnosis. And it was with that that I felt like I could see a path where if we really wanted to change the lives of these young children, we had to learn more about the disease. I felt so much like what we were doing was just treating the symptoms. And not really understanding the condition that led the child to have the medical problems that they had.

Stan

So, do you have a sense of what fraction of pediatric neurological conditions have a significant genetic component to them?

Joe

Well, we divide them up into those that are known to be environmental. We have a lot of causes that are traumatic maternal exposure to certain things make a sizable fraction, but I would say upwards of more than 50% of the children, especially those that present in the first five years of life or so, and now, you know that our field has developed a pretty good sense of when a child has the potential genetic condition or certain features about the presentation that tell us this is not something that is environmental. It wasn't due to the short stay in the neonatal ICU like everyone attributed this to. No, it wasn't they were in the NICU for a week or that they were born, you know, a couple of weeks early that has led to the problems. And with that, coupled with exome genome sequencing, we're now able to make diagnosis in upwards of half of the children that we see, and that's been tremendously rewarding to finally have the answers and share that with the families that this is the answer, this is the cause. It's not some mysterious thing. It's not because it runs in your family, or you somehow did something wrong when you were a mother to your child. It's in the DNA, you know, and that is both satisfying but also unsatisfying to a certain degree, we know the causes now, but we don't, you know, have the answers for how to treat.

Stan

So, you and I have lived through what people call the genomic revolution, and we all know that it really began in 1954 with Watson and Crick. And it really is an evolution. But just talk for a minute about the impact of genomic sequencing and how that's informed basically everything about medicine and including the neurology.

Joe

I think neurology, you know, more so than other fields, even genomics, has really touched it because we can't unlike in, you know, heart disease or pulmonary disease or renal disease, we don't have a good way to assess the brain. We can do MRI scans or EEGs, but we needed to have another kind of an orthogonal picture of what was happening with the patient. And genomics has really started to fill that space, and in the future, we might see other forms of omics. Transcriptomics or metabolomics and those kinds of things. But Genomics has really had a huge impact in the field of both adult neurology and child neurology. And I think it's not really something that's taught so well in medical schools, and probably a lot of physicians are still learning about it. You know, it's a journey for these doctors. But the doctors need to understand, and they are learning more and more about it in day-to-day practice.

Stan

So just for a minute, let's talk about what a genotype actually is. What does that actually mean?

Joe

Well, we have around 3 billion DNA bases and each one of those bases can take any of four different letters. The genotype is your letter at a particular position in your DNA strand across your 23 chromosomes. That means there's a lot of different genotypes each person could have, potentially billions of individual genotypes, whole genome sequencing sequences. Every single one of those letters, and that's been the revolution in the last 10 years or so. That's really allowed us to peer into someone's DNA makeup and given us a window into disease that we never had before.

Stan

So, a genotype then is basically the totality of a person's genetic capability. I suppose you'd say.

Joe

Well, there's a genotype and then there's the genome. So, we hardly use the word genotype anymore unless we're talking about a particular cause for a disease. We might say you have a genotype that predicts you're going to have Huntington's disease or Tay Sachs or breast cancer or something like that. But now that's in the context of all 3 billion bases. And so what I see where the field is going in the future is understanding not just the individual cause for the disease that's presenting in front of the doctor, but what does the rest of the genome tell you about how you might respond to certain drugs using pharmacogenetics or how your family history might intersect with your genome to predict other disease risk to the person, or not just the person, but also the person's offspring. You know, we're very interested in our research lab. We're studying the origins of new mutations that arise, and so someone's genetic makeup might be perfectly fit, but then their child might have a new mutation and we really want to understand the causes of that. So, we can think about ways of preventing those things.

Stan

So, the other word that we hear a lot about is phenotype. How does genotype create a phenotype and then inform the body as to what it's supposed to be and do and what it should do better?

Joe

Of course, as you know, there's Mendelian genetics in which your genotype perfectly predicts your phenotype. In other words, if you have a certain DNA base, there's almost 100% certainty you're going to have this condition as a result, and those are the ones that my laboratory mostly works on, and those are the ones that I think where those genotypes have the best predictive power for disease risk. And then there's other sorts of genotypes that can change your risk for a disease but don't predict with 100% certainty you're going to get them. And in the future, I think as all of this genomics is coming together, the field is going to do a much better job of being able to predict phenotype, in other words disease, from genotype. Those correlations are still kind of weak in many fields, but improving and this is where we're going to see huge investments, I think, from the NIH, and pharmaceutical industry, and lots of other players.

Stan

So, there are common genetic mutations and there are uncommon genetic mutations and I think everyone is familiar with common diseases, rare diseases and ultra rare diseases and whatnot. How frequent is it that there's a patient who has some mutation that just seems unique to that person in the entire world? Is that a common occurrence, or how often would you expect to see somebody like that?

Joe

Very common, surprisingly common. In fact, that's one of the criteria that we use when we're evaluating mutations. If it's not seen previously in healthy people, then it's more likely to be causing disease. Of course, there are founder mutations we always talk about the founder mutations for Tay Sachs or Broca or other conditions, cystic fibrosis. Those mutations have been documented decades ago. And we know that they're more common than we would expect by chance, probably because there's been some environmental influence that has provided some benefit to having those mutations like we know for sickle cell disease, for instance. But for the most part, human disease is due to rare mutations, we think. And as a field, geneticists are trying to classify those mutations, so we know what they look like, we know how to spot them, and we can label them all, give them a name and a number so that when we see them again in another person, we know that's the cause. But still, there's going to be lots and lots of mutations that come up that this is the very first patient with it, I'd say 90% of the mutations that we identify, they're unique to that one person and it creates a huge unmet medical need.

Stan

I mean, in the first instance just how do you figure out that that person has a unique mutation? I mean, if you've never seen anything like it before, how do you recognize it? How do you fit that into your differential diagnosis?

Joe

Well, this has been the whole field and experience from the whole field in genetics because the path is usually you find one mutation that looks like it makes sense, we check to make sure every diseased person in that family has that same mutation, if they don't, we throw the mutation out, it can't be the cause. And then we compare the notes with our friends. And now there's great databases that allow us to compare worldwide every patient with a certain disease that is presented with a certain DNA mutation, so there's a difference between the DNA mutation and the gene in which it occurs, of course. So, a lot of these unique mutations are occurring in genes that are previously linked to disease or maybe even new to that disease. But I think as a field, we're gaining an appreciation for how the granularity of the mutational landscape that produce, you know, rare diseases.

Stan

It’s amazing. So, you just recently published a paper that talked about mutation, directed treatment and mutation directed medicine. And, you know, I think most folks think that these names of diseases that we use commonly that were created centuries ago, that just described what a patient looks like when they progress far enough to be sick means something. But I thought that paper was very insightful because I think it points to the future of medicine, which is an action-oriented definition of a disease. You want to talk about that for a minute?

Joe

 Yeah, we're really excited about this concept and what led to that paper was my own experience and the experience of my lab seeing therapies developed for rare mutations. And we wondered how common would it be for a given mutation, that it could be treatable with an individualized antisense or gene therapy, and so we downloaded the entire human mutational database, what's called the ClinVar, that we had access to, and around 2 million known human mutations. And we found that over half of them, there is a viable path to a therapy which was shocking for us. We had no idea that there was going to be potential therapy for roughly half of the mutations that we think about. That paper is not actually published, it's on bioRxiv. But we hope it will appear soon. We've gotten a lot of feedback from people. They like the paper. It's had thousands and thousands of downloads now. And we hope that it starts to change the way doctors and patients think about disease. Ultimately, we like when a doctor orders a genome on a patient, that it doesn't just say we found the cause here it is, it says we found the cause here it is, and we predict that it might have a treatment for you.

Stan

So now you have a name of a disease that matters because it's an actionable name. You have a disease caused by this mutation in this gene and with your algorithm, and as it progresses and gets more sophisticated, and here's a possible solution for you.

Joe

Right, well the field of medicine is based upon that whole premise. We don't just diagnose; we diagnose and treat. But for genetic diseases, for a long time, we have lacked that possibility. And this is why so many people are excited about gene therapy and all of its various forms includes viral, and ASOs, and CRISPR, and lots of other things. So yeah, it's a really exciting time in medicine.

Stan

Well, of course I very much appreciate the fact that given how busy you are, and how many different hats you wear, that you've chosen to join n-Lorem as Chief Medical Officer. And I think most folks know now who are tuning in that n-Lorem’s mission is to take advantage of the technology that was created under my leadership, ASO technology, to provide personalized medicines, ASO medicines, for patients with these nano rare diseases, n of one kinds of patients, for free for life. But I'm anxious to hear why, given all the opportunities you have to for ways to spend your time, why invest in n-Lorem as you have?

Joe

It's in my gut. I feel this is the way to go. I spent the first 10 years of my career training in medicine. The next 10 years, developing ways to diagnose patients with genomics, but none of it has led to therapy, meaningful therapy I feel. And I was at a talk a couple of years ago a Gordon Conference, where the leaders in genetics were there, and we heard about this amazing drug for spinal muscular atrophy, and that just opened a lot of eyes like, wow, there's a therapy for this now. And this was of course developed at Ionis. And one of the audience members was an employee of Ionis, and I asked them, why don't we just personalize these drugs for people, you know, for all these mutations that we have? And I think back in that moment, for me it was an eye-opening experience to think about how all of this data and genetics we've been compiling for the last 10 years could be applied towards therapy. I can't think of a more exciting area of medicine. To me, I'm completely in. I'm really excited with the patients that we have enrolled. I am very excited every time I get to talk to a physician that has a patient that they would like to nominate, and I think that the outcome, we don't know, it's a giant experiment. We hope that the patients respond in the ways that we expect them to, but we're going to learn a tremendous amount from the patients who are our partners in this you know.

Stan

Well, I think we've all been stunned at the response to n-Lorem, and how many applications for treatment, and how many patients we've accepted, and how challenging it has been to try to meet all the demand. Does anything stand out to you as challenges that remain for us as we go forward to try to really broaden the benefit that we can bring one patient at a time.

Joe

What stands out to me is I think we're just at the tip of the iceberg. Yes, we've had a couple of hundred patients nominated, perhaps they've accepted 50, a growing number, but there's probably 100,000 patients a year that are getting whole genome sequence. If these mutations are really as rare as we think they are, n-Lorem has huge potential, and I don't know how it's going to scale. My main concern is we might be too successful and how are we going to manage? But I think we need to take it one step at a time, see how it goes, demonstrate to ourselves and to a skeptical community of patients, researchers and physicians just what we can accomplish and take it from there.

Stan

Yeah, well as the guy who led the invention of the technology, I can assure you it's scalable. All we really need to do is, you know, raise the funds to do it and put together the team. And I feel like we've got just an incredible team at n-Lorem, and that's the challenge that lies ahead, and the challenge that lies ahead is always the challenge that you created by solving the challenge that you've dealt with yesterday, right? So, wonderful to have you join us in that, and it's also delightful that we were able to visit and I'm sure the n-Lorem podcast audience will greatly enjoy this chat.

Joe

It's very exciting. Thanks for having me, keep up the great work. I think it's really important that we spread the news for patients with rare disease especially, you know, patients need to hear about it, doctors need to hear about it. And I'm just surprised how few people have really heard about it at this point. We need to get the word out.

Stan

Well, this is all a part of it, and it's all a part of the holistic care for these patients.

Narrator

n-Lorem is a nonprofit committed to discovering and providing personalized experimental treatments for free, for life to patients with genetic diseases that affect 1 to 30 patients worldwide, referred to by n-Lorem as nano rare. Many of these patients progress and die without ever achieving a diagnosis. This is where n-Lorem comes in. They do the impossible by providing hope, and for those that they can help, free lifetime treatment. For more information about n-Lorem, or today's episode, visit nlorem.org. Any questions can be sent in to podcast@nlorem.org. Search n-Lorem on Twitter, Instagram, YouTube, LinkedIn and Facebook to connect with us. Please rate and review the podcast on Apple, Spotify or wherever you listen. This truly helps us climb the charts and allows others to find the show. This podcast is hosted by Dr. Stan Crooke. Our videographer is Jon Magnusson of Mighty One Productions. Our producers are Jon Magnusson and Kira Dineen of DNA today. Thank you for listening.