**Q&A #1 with Patient Families**

# **Transcript**

Stan

Hello and welcome to the n-Lorem podcast series, a series that focuses exclusively on patients now referred to as having nano-rare mutations. I'm Stan Crooke, and I'm the founder, chairman and CEO of n-Lorem. N-Lorem is a nonprofit foundation that I initiated in January of 2020. Our mission at n-Lorem is to take advantage of the technology we created at Ionis Pharmaceuticals, antisense technology, or ASO technology, to discover, develop and provide experimental ASO treatments to nano-rare patients, and to do that for free for life. And today we're introducing an important new feature that I think will add some real value, and that is frequent Q&A sessions. We haven't quite decided how frequently we'll do it, perhaps quarterly. But these are opportunities for all of you who have questions to come to the source and let me attempt to answer them. Today, we are very pleased to welcome two parents of patients who have applied for treatment at n-Lorem, Amber Freed. Amber, welcome. Perhaps you can just quickly, I know most people probably know of you, but maybe you can quickly introduce yourself for our listeners.

Amber

Sure. My name is Amber Freed. I spent my career in equity analysis and had twins in March of 2017, the most beautiful twins ever. And very early from birth, I noticed that my son was not developing like his twin sister, Riley. After quite a diagnostic odyssey, he was diagnosed with an ultra-rare neurological disease known only by the genetic location SLC6A1 and I remember being extremely confused because my son was diagnosed with what sounded like a flight number and doctors told me nothing could or would ever be done because the disease falls into the bucket, too rare to care. I left my career immediately, and I have been fighting for him ever since.

Stan

It's very nice to meet you in person, and of course I'm well-appointed with the case and hopefully one of these days we'll be able to help and certainly we're working hard. at it. And in addition to Amber, Shanna Tolbert has also joined us. Shanna, why don't you introduce yourself? Welcome.

Shanna

Thanks for having me, Stan. My husband, Terry and I live outside of Atlanta, and I've always wanted to be a mom, and my daughter Ireland was born in 2015. And I love being pregnant, had an easy birth, but as soon as she was born, there were signs that something was wrong, and she went straight to the NICU. And I'll never forget, they did every test under the sun trying to figure things out, and a veteran NICU nurse said to me, "Something is wrong, we just don't know what." So, we took her home. She was delayed in every milestone, and then when she was six months old, she was sleeping on my chest because she was a terrible sleeper. And now I know why, and she had her first generalized tonic-clonic seizure, and I had never seen anybody have a seizure before, but I knew immediately what it was just because it was so extreme. That led to genetic testing, which revealed a CACNA1A genetic variant. And even at that time, doctors didn't know what to tell us that it meant. There was certainly no treatment, and very little information except for, you know, a handful of academic papers from various institutions. Anyway, I ended up making her a website because I had seen parent stories like Ambers, one thing led to another, got together with some parents and formed the CACNA1A Foundation. And I've since resigned, but it's a thriving organization that I'm happy to volunteer with.

Stan

Thanks very much. One of the surprising privileges of doing n-Lorem, for me, is that we, my wife Rosanne and I, have had the opportunity to meet a good many of the families that are involved, and we met with Shanna and the family in Atlanta last year. I'm hoping we'll make it to Atlanta again this year, and check in on Ireland and say hi again. Shanna, it's nice to see you again.

Shanna

You too. I can't wait to meet up again.

Stan

And the Braves are doing well starting the year, so I'm an Atlanta Braves fan, so that's good news for you Braves fans. The Rockies, I'm not sure about but anyway, so why don't we get underway on sitting here, game for all the kinds of questions. I know each of you have canvassed a number of others, so whatever your questions are, just get started.

Amber

I think when I was first starting, something that took me a lot of time to decipher was just to understand the process of how n-Lorem looks at cases, and how to apply, and from the patient point of view, who do we need on our team to apply?

Stan

Thanks for that question. And you know we've invested in a very thorough process that allows us to be certain that we're making very good risk benefit decisions for these patients. And we've recently rigged out our website, so hopefully it's a little better explained there. But the first step in moving toward therapy is to have a diagnosis. For a nano-rare patient, that turns out today to be a very difficult and challenging task. And many parents have to spend a great deal of time, unfortunately, identifying a site that can genomically sequence, and most of the time whole genome sequencing is needed, and then an investigator who is at an institution that would be willing to care for the patient with an experimental treatment. So that's step one, get a diagnosis, understand the genetics, and have a research physician who's committed and capable of caring for your child or yourself while being treated with an experimental medicine. Step two then is to go to our website and complete an application. And it really does require both the patient or parent, and a research physician, because there's a great deal of detailed information we need to decide whether it's appropriate that this patient be treated with an ASO. The next step, and we try to complete this in about six weeks, is we dig into the application, we get into the literature, we learn as much as we can about the case, and about the genetics, and about the phenotype of the patient. That patient is presented in detail to a committee called the Access to Treatment Committee. This is a committee made up of experts in the technology, experts in the organs and diseases that we treat, and it advises us about whether it's appropriate to treat that patient. That's a really important step. It's a very formal process that assures that this important decision about whether it's the right thing to do for the patient is made with full advice of really knowledgeable people. Once that's done, then we go to work, we try to complete the work within 15 to 18 months, but it's very variable depending on how challenging the mutation is. As you know, Amber, there can be some very challenging mutations that take longer, and we have to go back to the drawing board multiple times, but we keep working on the case, and in that time then we ask the parent and patient and physician to collect natural history data so that we compare what's going on before treatment to what happens after treatment when we have the when we have the ASO and begin treatment. Once we have the ASO, then the next step is to file an IND with the FDA. The FDA has to approve that IND, and then the institution has a what's called an Institutional Review Board. That again, is a committee that protects the patient and assures that patient is being treated appropriately. And once that happens, we begin to treat, and we do our best to assess the performance of the ASO in that patient. It can take as little as 15 months and it can take much longer. It just depends on how difficult the case is. I also want to answer about prioritization. We don't prioritize. The only prioritization we do is urgency. Many, many of our patients arrive on our door in desperate need. Of course, if they're at danger of succumbing to the disease, or losing an organ, they go on the top. Other than that, we think every patient should be treated equally, and we do our best to do that. We've been overwhelmed with demand. I thought by now we'd have a handful of applications and we're approaching 200. And so, we've had to grow much more rapidly. We've now tripled our lab space and facilities so that we can handle many more cases, and we're still behind. So we're not meeting our 18 month goal, but we're going to get there, and obviously how much we grow will depend on how much money we can raise. And so, it's a chicken and egg thing, but we are responding to demand as aggressively as we can, and we've been very gratified by the amount of support that we've gotten from so many quarters to allow us to grow more rapidly. Amber, does that, that's a lot of words, I hope I answered your question.

Amber

Yeah, it really does. I think from the parent perspective, you know your child is diagnosed with a bunch of word soup, and you have a doctor, and just the application process, it seems a little overwhelming at the time. And of course, the more information the better, but it definitely takes time and resources and advocacy from parents to be able to get that buy in from your physician to take the time to write the application, everyone is just always strapped for time.

Stan

You know that's a real problem and one of the disappointments, the challenges we have in identifying physicians and institutions who are willing and able to help patients. That is why one of our major goals is to encourage the introduction of genomic sequencing into newborn screening protocols. Only then will we actually know the prevalence of these problems, and only then will we get to patients early enough that we have a real chance to help. Before I leave this question, we also are confronted with patients who have genetic information that they found someone to do that they've paid to get, but they don't have a physician, and we do our best to try to find physicians and institutions that can help. If you experience that, do give us a chance, we'll try. We can't guarantee that. We're working very hard to create a set of preferred partner institutions and there it's just much more efficient, and we'll be able to do a much better job, and the application that comes to us will be complete on the first round and so on. So I think everyone has to understand this is brand new. This has never even been possible until we did it. And we are industrializing it. It is a large-scale task. We're learning as we go. And I wish I could say I knew all the answers to everything. We don't, we're learning and we're improving the process, and improving our communication to patients and parents as we learn more about what information they really need, and what they really want. One of the important things I'd say is if there's a gap in information that you feel, let us know, and we'll see what we can do to make the process more transparent and better. Our goal is to be as transparent as possible, but never over promise. We cannot promise anything except our best effort.

Shanna

So, thank you for that detailed explanation of the process starting with the application. Once a patient and family is accepted, what is the best way for them to track, and to know exactly where they are in the process?

Stan

The single best way is to talk to your physician. Physician, patient, parent communication is the vital length. And we never want to interfere or take the place of the physician in those communications. The most important thing is to be chatting with your physician. We keep the physicians aware of where we are. We're working on solutions for our website to make sort of steps in the process, and where we are a little more available to patients and parents. Right now, to my mind, the best thing a parent or patient can do is talk to the physician. We're available to those physicians seven days a week and we will provide the information that we can at that time. It's very difficult to define precisely how long each step is going to take. Remember, each patient is different. Each mutation is different. Each gene is different, and the demands for the ASO vary. There's no generic answer about how long anything should take.

Shanna

I experienced a little bit of a, like you mentioned, communication gap at the beginning, but once I reached out to you guys, you guys filled in the gaps, and it was super helpful. There might be patients who, and families who, are blinded, not getting their communication from the physician. I don't know if Amber's heard any of these stories. She's shaking her head. So, would you recommend that those parents just be more aggressive in their ask of the physician, and any advice there?

Stan

The first step is always to call your physician. Physicians are willing, they are, to communicate and frankly, how committed they are, and we're working hard to identify the really committed capable physicians so that we can recommend one. If that fails, then get in touch with us. We can provide answers in a blinded fashion, or we can provide answers in an unblinded fashion. The communication that we will be able and willing to do will still be limited because we don't want to get between the patient to parent and the physician. So, your core communication is with the physician, and if you're not satisfied with it, then you may want to talk to that physician. You may want to talk to the study coordinators or others who can help you. The really good institutions that are taking care of our patients often have teams, social service, all kinds of folks. And all of that can be very helpful. Again, there is no perfect answer because there's no perfect physicians, there's no perfect patient, there's no perfect n-Lorem, but these are the best answers I have for you today.

Amber

Thank you. What kind of frequencies, though should we expect because, of course, to the parents, every day feels like an eternity, and that is, in a year in the timeline of science, is a speck of sand. So, if we haven't heard anything as quarterly about appropriate to check back in.

Stan

I would say quarterly is about as frequent as probably makes sense. You're right, everyday matters, and every day seems like a year when it's your child or yourself. Don't forget of our first 173 applications 48 are adult. Our oldest patient is 67, so it's not just children, although the bulk are children. Each step takes the time it takes. But if you think about the fact that we must discover a new drug, the 30 years that it takes to discover a new drug for commercial development, what we're doing in this time is astonishingly rapid. Then we have to then do animal safety studies, and those all take prescribed amounts of time, 8 weeks, 12 weeks, and then they take other time where you can analyze the data and so on. So, there are just sets of times that can't be very mutable. They're required by the regulations that we have to do, so quarterly would be the most frequent, but I would say when you're anxious, if we can help you, we will. I know. So am I. I wake up every single day, and go to bed every single night thinking about my patients. And that's my privilege. It's your burden. It's my privilege.

Amber

Thank you so much for that, Stan, because I can only speak for myself, but I just feel like for my son, he's like a forgotten member of society. There is no place for him. It's just a single mom fighting as hard as possible for her son. And on the darkest days, it just means so much to know that there's somebody that cares. I admire your driving conviction.

Stan

Well, it wasn't what I planned to do at this stage in my life, but these patients are on here. Again, no one's at fault. The healthcare systems were created for the big diseases, common diseases. Only now do we realize how many of these nano-rare mutations exist, how many nano-rare patients. It's all unchartered water. What I will say is there's no one in n-Lorem who is in n-Lorem for any other reason than our patients. And our hearts are constantly out to the parents and patients that we deal with for the burden that they have to live with. We wish it were not so. I wish I didn't know the two of you. It would be better if you had happy, healthy children. There are people who care. You're not alone. These podcasts are meant to create a community out of this disparate group of patients and parents that I know are desperate and alone. We will work on it together.

Shanna

I definitely felt that when we met. It was a totally different experience going from having an approved application to meeting with you and your wife, feel that you're fully committed.

Stan

Not just I, every single person at n-Lorem. People left jobs that paid way better for this because we know these patients need us. We built a great team. I'm really proud of it, and we'll grow as quickly as we can to meet more needs. We know it's there.

Shanna

Well, I also felt that caring when I reached out to you guys about an article that came out with some ASO patients that experienced hydrocephalus, and you guys explained all that to me. Can you help people understand what their concerns should be?

Stan

And this is a really important question. What I want to do is, first of all, teach the sorts of things you need to know about a possible drug related side effect to actually speak, even cogently about it. And then get into NPH, which is the side effect you're talking about. But before I do that, I want to give you the short answer. First of all, anything you put in your body carries risk, whether it's food, natural supplements, drugs, and of course, experimental medicines are riskier. So, no one can promise absolute safety, but before you engage in an experimental treatment of any sort, and certainly an ASO from n-Lorem, you should sit down with your physician and discuss the potential benefits and risks in detail. Discuss the risks in detail. That said, normal pressure hydrocephalus in pH, in my view, based on our now hundreds of thousands of patients experience with a properly designed ASO that is optimized and dosed properly, NPH is an extremely low, generally avoidable side effect, I want to repeat that. With a properly designed, that means an ASO designed by people who know the technology, who've lived the technology, who understand the technology and have the judgments required to make a good ASO, and an optimal ASO, meaning an ASO that's gone through rigorous preclinical testing by people who have the experience to make the judgment about what is a good ASO and what is not. With that ASO dosed properly, I think NPH is generally avoidable. Now I'm going to give you the real answer. There are a half a dozen parameters that you must know about the side effect before you're even able to talk about it. The first is the incident. How many patients have been treated with the medicine, and how many patients have had the side effect? There's obviously a giant difference between an adverse event that happens once in 1000 patients versus one that happens to all patients. So, you need to know the incident. Next, what's the severity? There's a giant difference between the side effect that's life threatening, and the side effect that's moderate or mild. Third, is it self limited and reversible? There's an enormous difference between a side effect where you just stop the drug and everybody gets better versus a side effect that requires significant intervention to save the patient, incidents, severity, reversibility, and then you need the dose, and the dose regimen at which the side effect was observed. And finally, you need to look at the data and ask how solid the data are that say this is drug related. Sick patients have all kinds of things happen to them all the time, and so it's sometimes very difficult to know whether it's the disease or something else or whether it's the drug. So those parameters, incidence, severity, reversibility, dose, dose schedule, and strength of evidence are the things you have to know to talk about a drug related side effect. Now let's talk about NPH. There are two types of hydrocephalus, high pressure, and normal pressure hydrocephalus, you know that your brain and your spinal column are protected by bone. And that's a good thing. If you bumped your noggin to be the end of you, you didn't have your skull, right? But that bony structure creates a very limited space, right? And so, in that space, you have your brain and spinal column. And then you have the fluid that bathes the brain and spinal column, and provides nutrients, and gets rid of waste. That's called cerebral spinal fluid. Cerebral brain, spinal, the spine, the fluid that provides nutrients to your brain and spinal column. So, you've got a very narrow small space in which you've got all this brain and spinal cord tissue, and then this fluid, the CSF, is made by the brain. It's not all like blood. It's more like plasma. It's got some salts, very little protein, a ton of glucose because you use a lot of glucose for energy in the brain, and really any cells, when you draw, it looks sort of straw colored, and it should be clear. The most common type of hydrocephalus is high pressure hydrocephalus. That can happen either because you're making too much fluid, or you're not able to clear it, so there's a block in the in the canal that gets rid of it. If you make too much or you can't get rid of it, that then increases the fluid. There's no place for that to be, to go. So, the pressure in the brain and spinal column goes up. That's almost immediately symptomatic. People with high pressure hydrocephalus get a terrible headache. They get blurred vision. They can succumb very quickly. The most common causes for that are infections, meningitis, the reason people really get sick with meningitis is their pressure in their CSF goes up. Also, inflammation. And then there are some congenital defects that can lead to hydrocephalus. Normal pressure hydrocephalus means that for some reason the pressure hasn't gone up. If you think about that, how could that happen? The only way that can happen is the brain shrinks. You've got a limited space if you create more fluid, and you don't increase the pressure. Then you must compress the brain. That's normal pressure hydrocephalus. Most degenerative neurological diseases causes you to lose brain tissue, and so very often on an MRI, you'll see what looks like increased CSS space because the brain is getting smaller. And so, most nerve degenerative diseases have an incidence of NPH that varies depending on the disease and the severity of disease. Anecdotal reports of NPH are very difficult to interpret. Is it the disease? Is it the severity of the disease or is it the drug causing it? And that's why you need to understand the strength of the evidence. The pressure in the CSF that you have normally is very, very low. It's about 5 to 15 millimeters of water. So, it's even less than venous pressure. But anything more than, say, 15 millimeters is considered high pressure. Now in the data that mattered the most in understanding the risk of ASO induced hydrocephalus, normal pressure hydrocephalus actually comes from the studies in about 800 adult patients with Huntington's disease. This was conducted with Ionis ASO by Roche. And the reason that information is so important is the well-controlled trial where these patients were treated for a minimum of 69 weeks. And so, it's really high-quality data. The background incidence of NPH in Huntington’s is 0.4%. In that file 0.6% of the patients treated with the drug had NPH. 0.6, it's very difficult to know if that's more than the background. But the evidence, I think, is pretty clear that it was drug related. So now we're getting into it. The incident in this well controlled trial was 0.6%. The three patients who experienced it out of the 800, it was found moderate, reversible. No intervention was required, and the dose at which it happened was a very high 120 milligrams every two-month dose. It only happened in the highest dose, so now we know. 0.6% versus 0.4% mild to moderate, reversible, at a high dose 120 milligrams every two months, strength of evidence is solid. It's drug related. Now let's compare that to the ASO that produced normal pressure hydrocephalus. Two patients out of the two infants treated with the same ASO had normal pressure hydrocephalus. 100% incidents. 100% versus .6%, the side effect was severe and life threatening, not mild, not moderate, severe life threatening. The side effects required intervention, putting in chunks to get rid of the excess fluid. The dose at which it happened was 160 milligrams a quarter, very high dose. Ok, now you know, That ASO. 100% incidence severe, not reversible, at a dose that’s extremely high. Probably shouldn't have been used. Preclinical data on that particular ASO have never been presented in detail. But we have had the opportunity to gather a good bit of the information, and there's not a single ASO expert that I've talked to who thinks that that ASO should have ever been in the clinic. It was not a well-designed, not an optimal answer. And it was dosed at a dose far too high. Our limits normally are around 100 milligrams quarter, but much above that we really have to be convinced that the patient needs it. We don't intend to use 160 milligrams quarter. So, with a properly designed optimal ASO dose properly, NPH is generally avoided. Now, do you know how to think about side effects anytime somebody talks about side effects, your question should be what's the incidence? What's the severity? Is it reversible? What's the dose and what's the dose schedule at which it happened? Then you really understand what kind of risk you're exposing yourself or your child to. I know that's a lot of information on a long explanation. But this is really important for people to understand. Understand the risks as well as the potential benefits before you take a drug.

Shanna

So, Ireland is a little bit further down the list I think, and I know there are patients ahead, and I know that it's your intention to learn as much as you can from each patient in the process. If side effects are coming up, will those be communicated in real time to subsequent n-Lorem patients receiving treatment, or will we have to wait for the published studies to come out? How will we hear about those?

Stan

First of all, we have to be sure that we understand it before we communicate. So, the first step is to go through the process I just laid out to be confident that it's possibly drug related or not. Then, if it's a meaningful thing, we will issue a safety update that goes out to all of our investigators. We've already issued one and that was principally in response to NPH that happened with this other ASO, and the data that we had from Huntington's disease. And so, we're constantly watching all of the ASO's in the same chemical class to make sure that anything new that comes up will be communicated to our investigators and patients and so on. Then if there's a new side effect that we see that we think is a side effect that could happen with other ASO's other than the ASO we are testing, then we'll put that immediately into the informed consent. Unequivocally, we would not have patients or parents wait for a publication. Moving to publication, you know we've published now six or seven peer review papers. We're writing the most exciting right now, which is in January, we did a data cut off of the first 173 applications. There's no data that's ever existed like this. It's just going to be a paper that we'll describe the nature of these mutations, the nature of the, in the type how phenotypes vary, a whole slew of things that are literally unknown. And so, we'll be publishing data constantly. And that takes time. You have to collect the data; you have to write the paper and then it goes through multiple peer reviews and so on. And in addition, this year we began our first annual meetings in October, and that will be in Boston, and it will be a meeting for physicians, investigators, parents, patients. And that will give us a chance to give you the latest information we know as rapidly as we can get it in a detailed, thorough fashion. We're committed to making all of this available, and above all, every patient parent must have full access to any risks. And we're committed to doing that. We'll update that constantly. In fact, just before this podcast, what we were talking about is the process we'll be using to do that. No, it'll be immediate.

Amber

I have a question. I feel like a lot of us parents have a career in whatever, and we have to give ourselves an MD, scientific PhD overnight. So, for all of us citizen scientists out there, one question I had when I started looking at ASOs was understanding the difference between an ASO and gene therapy, and that one is permanent and an ASO is not permanent, but how long it takes to wash out. So maybe if you could just high level talk about those differences?

Stan

Step back for just a minute. People talk about cures. Drugs don't cure, they treat, and that's the great thing about drugs, because if you have a side effect, you can take the drug and stop doing it, stop giving it, and then the patient can get better. But if you take your Lipitor for your LDL, all your life, your risk of heart attack goes down a ton. So, drugs do great things, but they don't cure. And they're not permanent, and not permanent is a good thing. People tend to think that because you get something permanently, everything's going to be wonderful. It only is if you don't have side effects. ASOs administered in the central nervous system last about three to four months, and that's why when we begin dosing, we start at a low therapeutic dose and then raise the dose slowly to make sure that the patient is going to respond well to the drug. The side effects that typically will happen typically are shorter than three or four months, and we really try to avoid side effects. ASOs that are dosed subcutaneously, we dose every month, but we could dose every three months. So, these are kind of long-acting drugs. It's not like taking your Lipitor and having to take it every day. But they're not permanent. Gene therapy has the potential advantage of producing permanent effects, though that's by no means demonstrated yet. It has the problem of producing permanent side effects and you have to balance that. Is that something you want for your child or not? That depends on how safe that gene therapy is. If you think about a drug, you take it as often as you need to maintain effective concentrations. And so, if you get a drug every three to four months, that tells you how long the drug lasts every three to four months, your child will get an intrathecal administration of an ASO and with new ASO designs that are coming our way, we think we can lengthen that. So, we could do as much as every six months to a year at some point. But that's some time away before we get to those designs. I should also mention that the chemistry we use, and the designs we use have been studied now intrathecally for diseases in probably 15-20 thousand patients now. And so, we have a very good idea of how these things behave. And if you make a well-designed optimal ASO, it should be reasonably safe. The difference between an optimal ASO and a non-optimal ASO can be very large, so make sure you're working with someone who knows something about the technology.

Shanna

How are you defining optimal ASO? The word optimal, what does that mean?

Stan

It means different things depending on the target, but it means a process. And we've published, presented in many, many forms on our website, our process that we use to identify the optimal ASO. It begins with screening a big enough number of ASOs. So, we typically start with around 500 different sites in the target RNA. We're treating your child. So, that means we take that RNA that comes from that gene, and we design typically around 500 different ASOs, different sites. The reason you have to do that is RNA is structured, and when it's in its structure, it's very hard to get an ASO to bind to it, and they're also all kinds of proteins bound to it. So, what is the number of ASO screens? What is the process used to screen them? How rigid are the criteria to select an ASO to go forward? And then the next step, we look at a whole bunch of different potential things that we don't want in the ASO. Is it inflammatory? Does it have cytotoxicity? Those were all analyzed, and then we take a a good number typically 20 into rodent screening for safety. And then we take the very best and do you know, toxicology studies and only if ASOs passed all of those tests with all those different ASOs you think of as a giant funnel starting with 500 to 1000 different ASOs windowing that down to one. So, it's the process that makes it an optimal ASO. It's the experience, and it's the knowledge base, and that gives rise to the judgment about what's a good ASO that makes it an optimal ASO. And this is why I've repeatedly encouraged all physicians who want to make an ASO to collaborate with us. We're the people who invented the technology. We have 33 years. There's no one else who knows this technology like we do. So, an optimal ASO is made by an expert through process, it's rigorous and proven to work.

Amber

One thing that was quite a learning process for me was that just because you have SLC6A1 CACNA1A or Huntington’s, there are different mutations within a gene, and how treating one person can lead to breakthroughs for many more.

Stan

I think that's a really important point. In any genetic disease, what we now know is there may be a common mutation that many patients have, and then there will be an array of ever rarer mutations and those different mutations may have very different effects. And the different types of mutations. Is a toxic gain of function? Is a loss of functions? They can have tremendously different effects. And many times, a mutation requires an ASO design just for that mutation, and so it can be used for that patient and patients who have the exact same mutation only. And that's tough for parents and patients to hear. If this patient is getting treated, why can't my child be treated? And that's the natural response. Completely understand. But here's the thing to think about. Every single time we develop an ASO that works in a patient we learn something about all patients. And as we learn about that mutation, we then can go to work on the other mutations and see if there are ways that we can help that patient. And so, even if your child isn't the first patient to be treated with an ASO, what is important is that there's now focus on that gene, there's focus on that disease and we're going to be learning things that will help your child. It may not be the first child, but everything matters, and we'll do our best to help the next child along with the disease. That's really, really important. In our first 173 cases that we're writing this paper, we have quite a number of patients who have exactly the same mutation in exactly the same gene and somewhat different problems. And so, we're now learning that even the same mutation may produce a slightly different phenotype. All of that's important information, and the more of that we know, then the more of it we can design in, and we can identify patients better, treat them better and treat more patients. It is entirely natural to want your child to be treated first, but every child matters, and every child contributes to the knowledge that will allow us to help your child better. That's a tough thing to hear that your child isn't first. But it doesn't mean you're child isn't next.

Amber

I feel like rare disease just insights such as sense of anxiety and fear into parents that then you get to a treatment and you're afraid of your child being first. But you want them to be first. You know, there's no easy way to go about any of this. And it was quite a learning curve for myself that my son has a totally unique communication within the community. And then there are more active hotspots on the gene that are more easily studied.

Stan

And here's the thing. There's nothing good about any of this. I mean, I can't make any of this good. The right thing to happen is your child shouldn't have a mutation and shouldn't have a disease. So, what we have to do is make the best of it. And being the first patient is great, but it's also you're a primer patient and those patients occupy very special positions. They take more risk, and they provide beacons about what to do for the next child. And you know another question that I think I want to answer that's related to this, can we help patients who are so advanced that they are, you know, deathly ill? This was a question that I had in my mind when I started this. Because we know that many, many patients are arriving to us when they're really very desperately sick. And now we have, you know, both Anna, with the FUS ALS, who actually did die, had a cardiac arrest after she had a swallowing accident and still recovered. And we have Susannah, who's at KIF1A patient, and you may have seen her on various websites, who had progressed to being wheelchair fast and nonverbal who's now if you go look at the videos that their family, and her family has posted, she's playing, you know, throwing a basketball on the basketball court, and speaking in sentences and telling her mom and dad how to get up off the off the floor, being a girl. One important answer that I can give you right now that I couldn't give you a year ago is even the very severely advanced patients, and many times we may be able to help them. That's important for everybody to know. Not everybody can we help, but even if you are as severe as Anna and Susannah were, sometimes we can help. And it's that realistic hope that matters. Hopelessness is a terrible state for a human being, and we, at the minimum, want to give you realistic hope.

Shanna

We love hearing those stories. We're saying the same thing. So wonderful to hear.

Stan

And there will be stories where we fail. We're not going to succeed in every patient, but it's important to know already that it appears we can help the sickest of sick patients. We know that tomorrow you'll be worrying about your child the way you are today, and tomorrow's another day and another set of problems that you have to contend with, and we feel that every single minute of every single day we wish we could take that burden away from you.

Amber

I think a fantastic way to end this would be Stan talking about his favorite success story he's seen in his career.

Stan

Well, early in my career, you know, I built the first broad anti-cancer program that was successful, and I got into making drugs because as a resident, I had a patient, young man my age, who was referred with an abdominal mass, and ended up he had a disseminated testicular cancer, which was the most common cause of solid cancer death in young men. And I had to tell this fellow who just graduated from college, just got engaged, that he had at most six months to live. There was this experimental drug called Bleomycin, and then I got fascinated with it. So, I went to the company to work on that drug and built, they didn't have a cancer program, so I built it. And so, the first thrill I had was when Bleomycin, and another drug of mine, cis-platinum, were added. We took testicular cancer from six months fatality to cure. And at that time, I thought that would be the high point of my career. And I'm glad to say I was wrong. Because then, you know, I made other drugs, and they made a big difference. And then, I started Ionis, and you know, you're now like, there are 15 RNA targeted drugs approved. And Ionis says two more that are about to be approved, and SPINRAZA came along, and that's a miracle drug. Beginning those clinical trials was the scariest moment of my career because we were treating these babies that were almost dead. Anything could have happened. Think about all the children with SMA who are healthy. We know now if we begin treatment before symptoms, most of these children grow up like normal, healthy kids. How do you beat a normal, healthy child. And you think about the potential that's unleashed for those children and those families by this one medicine that I had the privilege of leading the development of. You can't imagine the the great feelings. And now with n-Lorem it's like returning to the practice of medicine for me. I get to talk to patients, I get to feel the patient. And I have to say, seeing Susannah do better, pretty damn good. And knowing that Anna's got a speaking tube, and her mom is able to hear her speak for the first time in three years, and she's going to school, and not needing a respirator, my goodness. What more can I ask? What more could I ask? And that's been my privilege. And it's my privilege to serve the nano-rare patients, you too. And the people you represent.

Amber

That's enough to make me cry.

Stan

That's okay too. These are reasons to cry for happiness, and there are plenty of reasons to cry for sadness. We appreciate your joining us, and we appreciate your patience, and I hope that everybody feels that this session is useful. And if it is, we want to hear from you. If you want to see changes in it, that would be great, and we'll talk next time. And I'm sure there'll be a lot of other interesting and good questions and hopefully some good stories to tell.

Shanna

Thank you, Stan.

Stan

Thanks everybody. Appreciate it.

Amber

Thank you.

Narrator

N-Lorem is a non-profit 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 into podcast@nlorem.org. Search and 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.