**Transcript**

**A Diagnostic Odyssey: The UDN and n-Lorem's Roles with Dr. Francis Sessions Cole, III**

Stan

Hello, I'm Stan Crooke. I'm founder, Chairman and CEO of n-Lorem. Welcome to the n-Lorem podcast series in which we focus exclusively on the needs of patients who are what we refer to today as nano rare patients; patients who have a unique mutation, often the only patient in the world with that particular mutation. Today, we are very privileged to have as our special guest Dr. Sessions Cole. Dr. Cole is the Park J White, MD, professor of pediatrics and professor of cell biology and physiology. He is the vice chair of the Department of Pediatrics and the vice chairman for Children's Health of the Division and the division chief of Newborn Medicine at the University of Washington Medical School in Saint Louis. Doctor Cole, thank you so much for joining us today and welcome.

Dr. Cole

Thank you very much, Stan. It's a pleasure to be here.

Stan

So, you've got this enormous title, but I think maybe to start with, maybe you can tell our listeners what you do every day.

Dr. Cole

So, Stan, I'm a baby doctor, a doctor specifically for sick babies, otherwise professionally known as a neonatologist. So, I see patients who are the smallest and the sickest in medicine, and many of them have a whole variety of problems. But a lot of them have lung problems.

Stan

Sesh, I know you trained at Harvard, but how did you come to be interested in being a neonatal pulmonologist or lung doctor?

Dr. Cole

Well, in the neonatal intensive care unit where my patients are hospitalized, they have very different problems. Some are very premature, some have infections, some encounter accidents of nature during the birth process, some have birth defects, but almost all of them have lung problems. And so, as a neonatologist, I became very interested in lung problems and made the observation that some of the children in the neonatal intensive care unit have lung problems that are based on their inheritance, or their DNA, or their genetics. And so, I became very interested in trying to understand inherited or genetically based lung problems in both babies and in older children.

Stan

I suppose in the lung, just like every other organ, there are frequent mutations but there were probably just a group of a limited number of mutations that really caused significant lung problems. Would you say, or is that just not right?

Dr. Cole

Well, in babies, because the lung is so important in the transition from womb to world, in human babies, the lung is the last organ to mature before delivery. Mutations that cause lung problems are in several genes but are very rare because these mutations, or changes in genetic code, reduce the ability of the baby to survive beyond the newborn period. Many of them do survive now thanks to the technology associated with the neonatal intensive care, but there are several genes that we've identified that have rare or novel genetic code changes that lead to these kinds of genetically inherited problems in newborn babies and in older children as well.

Stan

So, you know, we're interested in the sort of nano rare patient, the patient who has a mutation that's unique to that patient or unique to a very small number of those patients in the entire world. I'm sure you encounter those patients at some reasonable frequency, don't you?

Dr. Cole

Yes, we have a lot of patients in the neonatal intensive care unit who have lung problems and other problems like birth defects or metabolic problems who have novel genetic code changes. And these novel genetic code changes frequently one code change in 3 billion code numbers, can cause babies to have progressive breathing problems and in some situations, rare, without a lung transplant, they cannot survive beyond the neonatal period, the first 28 days of life.

Stan

So, what fraction of the patients you see on a regular basis actually end up requiring a lung transplant?

Dr. Cole

We see approximately six babies a year out of a total admission pool of about 1400 babies. So, a very small fraction nationally these babies, of course, are very rare, and we hear about many of them because we not only can help provide the genetic diagnosis for these babies and families, but we can also provide them access to lung transplantation if their families choose to pursue that particular option.

Stan

Is a lung transplant a cure?

Dr. Cole

So, a lung transplant for babies with genetic problems that cause them to have breathing difficulties is not a cure, it's a trade of an acute lethal problem for a chronic lethal problem. We've been very fortunate and have learned a great deal about lung transplantation for babies, but it is still, I think, a palliative intervention rather than a curative intervention for these babies, and we are very interested in trying to develop therapies that would give these babies better long-term outcomes than lung transplant.

Stan

But it must be very difficult because to create a medicine for one baby in as the number that you gave, it would seem very, very hard and of course that's the area that we're interested in at n-Lorem. Are there any medicines that are useful today that you can use in these babies?

Dr. Cole

We have tried a variety of medicines that in older children and adults may work, but quite frankly, these medicines are nonspecific and predominantly ineffective. And so, we really are left with the situation, which is a difficult problem for us as providers as well as for the families of these babies. We're left in a situation where we have really not very good choices. Choice one is to see if the baby can survive until lungs are available, and as you can imagine, availability of infant lungs is very scarce. Or option two is what we call a palliative care, and in that situation, families choose not to subject their babies to the prolonged, painful interventions of being in a neonatal intensive care unit, and those babies pass away.

Stan

That sounds terrible, and so you're dealing with these brand-new babies who are terribly sick and you're having to support them with the breathing machine and all of that, and to a large extent, you have very limited opportunities to offer these particular babies are real long-term solution.

Dr. Cole

That's correct, and it's very difficult. The one thing we can offer to families after the resolution of their baby, either a transplant or passing away, is that we can provide knowing the genetic code changes for a specific baby, we can provide some advice about the likely recurrence of the problem for that particular family, and therefore we can help them begin to consider, once the loss has become a little more manageable, what their options are to have an unaffected baby in the future.

Stan

It sounds like a really tough way to spend your days. How do you manage the just, the emotions of all the sadness around these babies?

Dr. Cole

It is hard, there's no question about that. But I would say that the resilience and strength of the families, of the babies, are very inspiring to all of us who care for these babies, and it's really the strength of the families that I use because I can't imagine what they're going through. And yet they are able to come to the hospital every day, see little changes in their babies that, you know, help them have hope. And so, I think it's very important to understand that these families have extraordinary strength and resilience and that strength and resilience really help all of us who care for the babies, support the babies, and support the families.

Stan

Yeah, you know that's very much my experience both in making medicines for large populations of patients and tiny populations, and now at n-Lorem is that it's just astonishing to me the strength and commitment of parents and to their children and the lengths that they can go to try to help and it's wonderful to see so many people come together and try to help these patients. Hopefully we'll be able to do a lot more as the future unfolds here with n-Lorem and other approaches that are taking place. I know that you've been extensively involved in the Undiagnosed Disease Network, and I think that's an important thing for our listeners to understand, and you know, with the groundwork that it's laid to help us begin to think about treating some of these patients. You want to just tell us how you got involved with the undiagnosed disease network, which we'll call the UDN to reduce the length of words, and what it does, and what's important about what they've accomplished in this program?

Dr. Cole

Yes, the UDN was conceived by Dr. William Gaul at the National Institutes of Health, and he recognized that patients, both babies and children, as well as adults would benefit greatly from a diagnostic standpoint with the new technology of being able to decipher every bit of gene code in every person who's undiagnosed. And so, he took that approach and was very successful for several years running a program that was just at the National Institutes of Health. And then Dr. Francis Collins, then the director of the National Institutes of Health, decided to support the expansion of Dr. Gaul's program across the United States. And currently there are 12 clinical sites who evaluate patients who have frequently been, who have been, almost always, an extensive and prolonged diagnostic odysseys up to 8, 9, 10, 12 years, and these patients have seen multiple sub specialists at multiple centers, have gone through a whole variety of diagnostic procedures, imaging procedures, blood tests and still, while they have objective findings of problems in their hearts or in their brains or in their lungs or in their kidneys, still do not have a unifying diagnosis. The UDN has really elevated the awareness of these patients both for the public as well as for insurance companies. In addition, the UDN has helped elevate the awareness of the importance of these patients across the United States, it's estimated that there are 30 million patients with undiagnosed diseases in the United States, and fortunately the UDN has leveraged subspecialty expertise integrating the expertise with very advanced state-of-the-art gene code deciphering strategies and has been able to make diagnosis in about a quarter to a third of these patients. And so, a diagnosis for these patients is a critical step in trying to figure out what to do for the patients. The diagnosis also gives patients access to other rare disease patients with similar diagnosis because they have the same gene problem. Being able to use social media to sort of come together has also been a very important part of what the UDN has done. And the UDN I think now has provided n-Lorem and other foundations with a group of patients whose specific gene code diagnosis is known, and hopefully that knowledge will help n-Lorem identify potential strategies for treatment.

Stan

That is a really great achievement, and it's taken probably about a decade as I recall. And I think it's important that our listeners know that it's only the fortunate few who make their way to the UDN, the vast majority of patients with the nano rare type diseases and that are essentially all genetically caused unfortunately progress in their disease and succumb to the disease long before they even have a chance to get diagnosed. It's just an awful situation and the n-Lorem effort has laid the foundation for the work that now is being taken on by many personalized medicine centers in addition to the UDN sites. Isn't that true?

Dr. Cole

Yes, there are 12 UDN sites, but just to give a sense of the mismatch between the achievements of the UDN and the need of patients, the UDN has evaluated a little over 5000 patients in eight years has made diagnosis in about 1500 of these patients, but there are still 30 million patients out there who need evaluation. And so, the UDN's strategies and approaches have been recognized, and to some extent adopted, by multiple other precision medicine centers, almost always at academic medical centers, where there are multiple sub specialists, there are resources for advanced imaging and other kinds of sophisticated diagnostic technology. The National Organization of Rare Disorders has recently recognized a number of centers around the country as being centers of excellence for rare and undiagnosed disease patients, and those kinds of centers are the ones that will hopefully help to begin scaling, increasing the number of centers available for rare and undiagnosed disease patients so that more of them can have access to these kinds of evaluations and gene code deciphering technology.

Stan

So, in simple terms, the patient gets referred to a UDN site, then the patients’ genetic characteristics are determined, the mutation is defined, the manifestations of the disease, which we can call the phenotype, is defined. And then, of course, the gene is functionalized so that we know, if we alter the gene function, what might happen, and all of that is done sort of patient by patient. Is that fair to say?

Dr. Cole

Yes, that's exactly right. Many of the patients have novel gene code problems and trying to understand how to rescue the problems that are caused by the gene code change requires a whole other set of scientists and investigators who can use model organisms, organisms like flies, fruit flies, worms, and small fish called zebrafish, and they use these model organisms because these model organisms can test the functional disruption that the gene code problem has for individual patients and then once that testing is done, we then have clues about the best therapeutic strategies that might be pursued to rescue the problems that are caused by the gene code mutation.

Stan

Well, it's an incredible achievement, but it is true that even with all those resources about a quarter to a third of the patients get diagnosed, the others don't. And how do you account for that?

Dr. Cole

I think that the fact that about two thirds to three quarters of the patients evaluated don't receive a genomic diagnosis is a reflection of how much we still have to learn about how genes work. We have very, very sophisticated techniques to try to comb through gene code results to identify those differences in gene code that might be responsible for individual patients’ conditions. We clearly have much more to learn about how to analyze gene code in addition, there may be other situations where an environmental, an unrecognized environmental problem interacts with a person who is susceptible because of the gene code changes, and we don't recognize the environmental problem that is actually part of the cause of the undiagnosed disease. So, we still have a lot to learn, but I am optimistic that with the progress that's being made now, we will continue to increase the number of undiagnosed patients who receive diagnosis in a reasonable period of time, as you say, before they succumb from their diseases.

Stan

That's great. And so, one of the key things that the UDN has achieved is it's generated a whole lot of data from which we're learning every day about why some patients are diagnosable, and others aren't. So, why don’t you tell us how you got involved with the UDN.

Dr. Cole

Well, I got involved with the UDN because at Washington University in Saint Louis, where I practice, there are many, many resources, people, diagnostic capabilities that are available, but they had not really been united under a single program and I was fortunate to sort of lead the efforts at Washington University three or four years ago to try to pull together those resources in an application to the National Institutes of Health to be able to become a site in the Undiagnosed Disease Network, and we were successful with that application. It's also part of my sort of own DNA that, especially for babies, but also for all patients, older children and adults, I feel very strongly that we all need, as providers, never to accept the fact that we can't find a diagnosis. We need to pursue the diagnostic possibilities in these patients because a diagnosis is so important for patients who are struggling with not easily classifiable problems that are both life impacting and sometimes life limiting.

Stan

You know, once you have the mutation sorted out, it doesn't really matter what you call the disease, the mutation then becomes the actionable event. That's your problem and this then gives us a target to fix it. So it is, you know, it's just a vital first step in ever treating a patient properly is to get to a diagnosis, and I think it's fair to say too that when patients feel they have at least a name to call their problem, that's also an important emotional step for patients. I'm sure you see that in your practice as well.

Dr. Cole

And I would say that patients who are struggling with an undiagnosed disease want to trust someone to help them find the answer for their problem, and one of the other characteristics of the Undiagnosed Diseases Network evaluation is that there is a trust developed between those of us who are trying to figure out a diagnosis and the families or patients who are affected by not having a diagnosis, and that trust is so important because as you might guess, especially for patients and families who have been on prolonged diagnostic odysseys, there develops sometimes some skepticism about what is really going to happen to me and what can doctors and scientists really offer me. So, we try to provide tangible, accessible hope for these patients who have been undiagnosed.

Stan

You know, of course, that one of the first collaborations that we did at n-Lorem was with the UDN. But I've been surprised and very encouraged that less than half of our applications have come from UDN sites. And I'm encouraged by that because that says many, many other personalized medicine centers are joining in the pursuit of solutions for these patients and that's great. But my feeling about a mutation diagnosis is that as a general rule, the answer that has to be given to the patient is there is no treatment today for you, and I'm sure that's very disappointing for patients to hear even when they have a name for their problem.

Dr. Cole

It's very disappointing for patients and quite frankly it's very disappointing for those of us who are taking care of the patients because a diagnosis is critical. But almost every patient and family ask me as soon as we find a diagnosis, "Now, what do we do?"

Stan

And of course, that's where n-Lorem comes in, and we offer, you know, genetic medicines that so we take that mutation once we know the mutation, we can fix it in in many cases. And of course, the medicines begin. Since they're genetic medicines, we designed the medicine to address that particular mutation and your involvement in n-Lorem has been a really critical part of our success at n-Lorem to date. You know, I should know, but I don't really know exactly how you came to be so involved with us.

Dr. Cole

Well, I was very fortunate to be asked by Dr. Joe Loscalzo, who's involved with n-Lorem, to serve on the Access to Treatment Committee, and n-Lorem is really pioneering the kinds of processes that are so necessary to link a therapy with a genetic diagnosis. The Access to Treatment Committee includes sub specialists from many different many different areas who come together and pool their expertise and experience to try to figure out what might be the best therapeutic approach for a gene mutation that is novel, that has never been seen before, and these kinds of discussions are so important and quite frankly, are novel across the country. They must include a rigorous understanding of the gene mutation and what the gene mutation does. They must include a rigorous understanding of what is happening to the patient, and what symptoms and signs can best be used to evaluate a potential response or the effectiveness of a possible therapy. And they must include also understanding of what it will take from a regulatory and ethical perspective to be able to provide a test therapy for a novel genetic disease.

Stan

Well, you know at n-Lorem our focus is on the n of 1 type patient and to identify experimental ASO treatments, our technology, that can be used and provided to these patients for free for life, and we are grateful to be able to do this we are, of course, of a nonprofit foundation, as you know, well. And one of the things that I felt was so important in putting n-Lorem together was to assure that each step in the process was of the highest quality possible, because what we can't do is treat these patients in ways that are cavalier. We must know what we're treating, why we're treating, and how we're going to measure the benefit that we hope to see for each of these patients and the Access to Treatment Committee is comprised, as you said, of all of these types of expertise, plus expertise in our technology. And so, it's an incredibly valuable support for these patients and for me. Because the recommendations from the ATTC come to me and I make the final decision, what patients we treat. And we've been very busy in contrast to what I expected, which was a few applications, we're now approaching 130 applications and we're proceeding toward treating, you know, as many as 50 of these patients, which is a remarkable number. If I force you to say two or three things that You've learned that are the most important to you out of your experience in ATTC, what would you say?

Dr. Cole

I would say that the first thing is that, as you've referenced, the quality of the scientific approach must be impeccable. And what impeccable means is that we need to be sure that what we're going to propose to do for our patient therapeutically is safe and effective. And all of us want every treatment for these undiagnosed patients to work the first time without any ambiguity. However, we can't let our bias about wanting the treatment to work to cloud our judgment when it comes to ensuring that we have objective metrics with which to measure the effectiveness and safety of the of the therapy that we're proposing. So, I think that kind of tension between wanting to be able, successfully, to treat a patient, and knowing that we have objective findings that will tell us when the therapy is not working, is so important.

Stan

And so, you're comfortable with the systems we put in place at n-Lorem?

Dr. Cole

Absolutely. I've learned so much about the multiple dimensions of the process of evaluation of the patient, evaluation of the mutation, and evaluation of the possible therapeutic approaches. It's been so important for me as an individual because when I speak with families and patients, I need to be able to help them understand what the process is, what the challenges are, and what the potential, both downsides and successes, are going to be if we can develop potential therapeutic approach.

Stan

Well, Sesh, thank you very much for the opportunity to have you participate in this podcast series and much more importantly for your commitment to patients that we care about, and you care about, and all the help that you've provided n-Lorem over the brief two-year history that that we have, we couldn't have done it without you and your colleagues on the ATTC. And so, I'll open it up to you for any final comments and then we'll close this podcast, and it's been a great privilege to get to know you and I'm sure our audience feels privileged to get to know you a bit in this interview. Any final words for us?

Dr. Cole

Well, Stan, thanks for your kind words. I would say that n-Lorem is doing pioneering work in an area of enormous need, and I am privileged to be a small part of that work.

Stan

Thank you so much, and thanks everyone for listening to this podcast. We hope it's been informative for you and it's certainly informative and inspirational for me.

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 into 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.

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