The Rare Disease Gazette

Conversations with the world's experts about rare disease

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COMBATING THE FRAGMENTATION

FONDATION IPSEN
BookLab

Editorial

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Rare Disease Detection: Rare But Not Alone

The plight of patients with rare diseases is a critical unmet need of patients in healthcare. The statistics are frightening; there are 7000 rare diseases in the world that affect 350,000,000 people. One in eleven Americans has a rare disease. Three-quarters of patients with rare diseases are children and only half of patients receive an accurate diagnosis. The average delay for a patient to receive a diagnosis with a rare disease is 1 1/2 years. It is deeply concerning that one in four patients with a rare disease waits four years for an accurate diagnosis. There is an urgent need to communicate knowledge and expertise in the field of rare disease detection.

The journal *Science*, (American Association for the Advancement of Science) in collaboration with Fondation Ipsen delivers international science webinars for the general public.

In 2022, these webinars focused on building solutions to improve the detection of rare diseases. *The Rare Disease Gazette* is a magazine that broadcasts these discussions.

James Levine

FONDATION IPSEN

DON'T MISS!

The Conversation

Experts of the month: Sean Sanders, PhD, hosts a conversatio with world's experts about Combating the fragmentation of data and disciplines: Innovation hubs to address rare diseases

The Conversation

Experts of the month

Zizi Imatorbhebhe, M.B.A., M.S., P.M.P *(ERGOMED PLC, Raleigh, NC)*
Anna Lehman, M.D. *(University of British Columbia and Vancouver General Hospital, Vancouver, Canada)*
Vinodh Narayanan, M.D. *(TGen, Phoenix, AZ)*
Sean Sanders, Ph.D. *(Science/AAAS, Washington, DC)*
Marshall Summar, M.D. (*Children's National Hospital, Washington, DC)*

Sean Sanders *(host)*:
A warm welcome to this second science webinar in our 2022 Science and Life series on rare diseases. This webinar is entitled Combatting the fragmentation of data and disciplines: innovation hubs to address rare diseases.

Marshall Summar:
My name is Marshall Summar, I run the Rare Disease Institute at Children's National Hospital here in DC. I have been in the field of Medical Genetics and rare disease since about the mid-80s. It has been fascinating to watch all of the evolution that has been going on in the field.

Zizi Imatorbhebhe:
I am Senior Vice president for Global Strategy and Development. I also head our Rare Disease Innovation Center at ERGOMED, which is a UK and US-based clinical research organization. I have been in the industry for over 30 years, and in the rare disease space for quite a number of years. I am also a published author and speaker in the rare disease space. I am really glad to be a part of this conversation.

Anna Lehman:
I am an Associate Professor at the University of British Columbia in the Department of Medical Genetics. My research has been focused on improving genomic diagnosis for patients with rare diseases. I have a clinic in Vancouver General Hospital focused on the care for adults who have inborn errors of metabolism, and my lab is at the BC Children's Hospital. We are all part of the same academic healthcare network.

Vinodh Narayanan:
I am a child neurologist. I work here in Phoenix, Arizona, in the USA. I also direct the Center for Rare Childhood Disorders at an institute called TGen. TGen is a private non-profit research institute which focuses on bringing the tools of genomics to diseases, primarily cancer, but we also launched the Center for Rare Disorders, graduating from SNP arrays to whole-genome sequencing in 2011. I am glad to be part of this panel. Thank you.

Sean Sanders *(host)*:
Marshall has alerted me to the fact that centers of excellence and innovation hubs are not always the same. Marshall, could you explain some of the differences?

Marshall Summar:
Admittedly, there is a bit of semantics to it. In rare diseases, a center of excellence is based around clinical capacity. In other words, Anna's program in Vancouver has a deep capacity to do a lot of things for patients: you would expect the ability to care for kids, adults, having all the secondary specialties, all the things you would need to care for a patient. An innovation center doesn't necessarily have the clinical chops, but is a place where they are focused on the research, developing new products, new strategies, new treatment protocols for patients. While the two can overlap, they can actually be quite separate entities.

"In rare diseases, a center of excellence is based around clinical capacity. […] An innovation center doesn't necessarily have the clinical chops, but is a place where they are focused on the research, developing new products, new strategies, new treatment protocols for patients. While the two can overlap, they can actually be quite separate entities."

Sean Sanders *(host)*:
Zizi, could you talk a little bit about what do you do at ERGOMED and how you fit in with those definitions?

Zizi Imatorbhebhe:
Absolutely. As I mentioned, ERGOMED is a clinical research organization. Our focus is primarily on oncology and rare disease. I head the rare disease efforts and our rare disease innovation center, so we actually have an innovation center. What we do with the innovation center is to work with a variety of industry partners to address the various challenges in rare diseases. Obviously, as in rare disease drug development, there are many different challenges in trying to bring an assay through the life cycle, because we are dealing with such small patient populations, lack of end points, lack of natural history, etcetera. Our innovation center really exists to look at the challenges and the problems in rare disease and drug development, and bring the best partners forth. For example, we might be looking at a study that involves children. In this case, we might be looking at bringing in a single control arm to minimize the use children as part of a randomized trial. So we will bring in the best partner that provides that kind of information, or that kind of service, into the equation. That is how we use our rare disease innovation center: to leverage the best minds, the best services, the best partners, to help us address the many problems in rare disease drug development.

Sean Sanders *(host)*:
Great. Vinodh, maybe I could come to you next to talk about what TGen does. Would you partner with an organization like ERGOMED, or do you have your own innovation structure at TGen?

Vinodh Narayanan:
I think TGen has a unique situation, because it is not a major medical center: we are not a big university like the University of Washington, the University of British Columbia, or even a big hospital like DC Children's. We are a private non-profit research institute. It was created by recruiting Jeff Trent, who I think was a Vice President or a Vice Director of the National Human Genome Research Institute during the days of the Human Genome Project. Jeff being from Arizona, he was enticed to return to the state and created TGen, with the primary mission of bringing genomics to people, by developing a collaborative center, and that is really what it has become. Since it is not a hospital, everything is done on a collaborative basis. The center that we launched in 2013 is actually the first clinic that operated completely at TGen.

Initially, part of our mission was in diagnosis. I would think of our center as an unaffiliated copy of the Rare Disease Network or the Undiagnosed Disease Network that was set up at the NIH – except that we mainly have been serving the population around Arizona. Anybody who would like to enroll in our research study can just reach us through our web page - I have a couple of clinical research coordinators who do all the intake. If there is a suspicion that there is a genetic basis for their disorder, then they will get enrolled. We usually start off with a whole genome and whole transcriptome sequencing to pinpoint what the problem is. As this technology has become more widely available, we have shifted our focus to the 60% or so of cases where whole genome sequencing does not give an answer, as well as to treatment. I direct a small research lab where we select a few conditions that we have been studying. That means studying biology and new ways of approaching therapy. Rett syndrome is an example of a disease that I have been studying for many years. We have a biorepository where we collect skin fibroblasts on hundreds of our patients. We are very open to sharing them with investigators around the world who are expert in a particular gene. I think we have been greatly helped by the collaborative environment created by GeneMatcher particularly, which allows us to connect with scientists who are working on a particular gene and help us to help our families.

Sean Sanders *(host)*:

Anna, let me give you a chance to jump in as well and give your two cents.

Anna Lehman:

What we are developing in Vancouver is very similar to what Vinodh has developed. We are seeing the principle in evolution which states that when the same adaptations are happening in different places, it means that that is what we need. In our hospital, we found that we are now having great access to next generation sequencing, exome sequencing, for diagnosis - it is quite equitable in Canada, thanks to our public health care system. But the next problem we had was a variance of uncertain significance, some of which looked quite compelling. You can tell that the majority are probably not relevant. However, some of them really needed more evidence to kick them over to a diagnosis for the patient. Therefore, we created what we call a Discovery Hub, to connect our patients with the expert in that gene around the world. We have a platform or infrastructure whereby we can provide consent and material transfer agreements, resources for collecting samples, creating cell lines, shipping, tracking in a very coordinated and safe way. This was a huge improvement to our center because clinicians have great ideas, they make these interesting findings for patients, but they lack the time and capacity to create new protocols de novo and to ship things off from their desk.

Over time, our hospital has become much more careful about using dollars allocated for clinical care for any kind of research. That has also been a shift: there is a lot more careful accounting and auditing, so we needed a formal infrastructure to support that kind of patient-specific research. It did not fit into the classical kind of research study where you have a large hypothesis that you are trying to develop. We just wanted to help individual patients, so we created a hub to achieve that. The question is, how can this be funded? We have a research institute attached to our hospital that has a foundation that raises funds. This is a pilot to see how much it is meeting the needs of our patients. So, we do have funding that was fundraised that will last for a few years while we explore. So far, it has been fantastic. The biggest things that we have been able to offer are RNA-seq to look for the potential of splicing.

The second thing that has been most helpful is simply growing these cell lines and then sending them to the expert around the world that has developed the functional assay to test that variant. In some cases, we have not just variants of uncertain significance, but also novel genes. Sometimes it is a scientist in our institute who is going to do animal models and much more extensive work, and then GeneMatchers plays a major role in getting the cohort that is needed. That is the recipe these days. That is what we are working on here. It is very similar to Undiagnosed Disease Programs in the states, but it serves our patient population so that they don't have to travel to the NIH or somewhere else. It is working out well so far.

Vinodh Narayanan:

We are close to the southern border of the United States, and we have also recruited many families from Mexico. The Sonora state is very close to us, and they don't have the resources that are available here in Arizona. Unfortunately, because of IRB protocol, we are not allowed to do the consent over the phone, as patients must be in the United States when we consent them. But the great thing is that all of our efforts are supported by philanthropy, so we have never asked any of the 700 or 800 families who have been enrolled for their insurance information or a credit card. I think that we are fortunate to be able to do that. It certainly applies to the people who come from Mexico as it is not affordable for them.

Zizi Imatorbhebhe:

About your initial question about the difference between innovation hubs and the Rare Disease Centers of Excellence: it will greatly depend on the entity that is actually starting it. In a clinical setting, for example, in a hospital, it will look a little bit different than when a patient advocacy group or when an industry organization sets it up. If you are just from the clinical environment, for example, your center of excellence looks different. If you are from the industry, your center of excellence or your innovation hub also looks different. The FDA, a regulatory agency, set up the Rare Disease Innovation Hub with NORD, which is a patient advocacy group, as well as CPAC - another innovation center. I think that viewers should keep in mind that the differences will really depend on the entity that is setting them up as well.

Marshall Summar:

What is great is to see all the innovation going on out there. They declared only about two months ago that they think they had finished sequencing the human genome. It is a discovery period. So while we are using a lot of this information clinically, I think my colleagues here might actually say that a lot of times, the most common answer we give a patient is "maybe", "We think this change we found probably causes this". But now we are doing the background work and sharing these cell lines, sharing this information... One of the things that has really been encouraging about this field is that people are sharing their data. When they find a new change and they have a clinical presentation with it, that data is then put out there for other people to look at and say "Ah, we have seen the same thing." I would say we are at the edges of the puzzle. Right now, we have a ton of pieces to fill in in the middle to move forward. These are the types of efforts moving forward that are going to get that done.

"One of the things that has really been encouraging about this field is that people are sharing their data."

Sean Sanders *(host)*:
Anna, what do you see as the really critical issues that innovation hubs can address?

Anna Lehman:
We must figure out a way to share our data more. In Canada, we have provincial health care systems: we have a collection of separate healthcare systems. There is a project being led by an organization called Genome Canada, called All For One, which is trying to get data sharing happening across these provincial boundaries, primarily through the genomics laboratories that are the stewards of a lot of the genomic data. Initially, that will tremendously help with the diagnostic process and sorting out variance. We also hope that there could be a broad registry across the country, that would enable any researcher who is interested in a disease to find all the patients in the country who have that condition at once. That is a lofty goal, but that is the next step. That work is starting to happen, largely with privacy and legal specialists, around data sharing, privacy access and so forth. That is the next direction where we are headed: how to link our individual centers of excellence together more robustly.

Marshall Summar:
Anna, one of the challenges we run across with next generation sequencing, and with a lot of the interpretation, is actually having a good phenotype. I know there have been some things around human phenotype ontology... Where do you see that going? The sequence is a giant lever, but you must have a fulcrum for it. So how are you all working on that?

Anna Lehman:
That is a very good question. We are trying to integrate tools that try to make it easy for the clinicians to input phenotypic information. Characterizing phenotype is not a problem - we have excellent clinicians in these centers of excellence. The problem is: how can we extract the records into a portable format in a time-efficient way? We are hoping that there are software solutions to make that happen, so that we are not just having high level HBO terms that are not helpful for a more granular analysis. That is another challenge.

Vinodh Narayanan:
I am a clinician and a self-taught geneticist and bioinformaticist. I think phenotype is absolutely critical. Without that information, it is extremely difficult to make sense of this massive amount of data. This just reminded me of a call that I was on several months ago with FDNA. Of course, they are geared towards capturing a single picture of the patient, a frontal view, and generate a differential diagnosis along with terms that you enter into their patient database. I mentioned to them it would be great to have a video input because, at least as neurologists, we would greatly value a video clip that shows what the patient's behavior, movement or speech is like. I think that it might eventually come to that: a video image that is uploaded into some program that extracts all of the phenotypic data, and that can automatically get into the next generation sequencing analytical tool. I am hoping that will come true.

Zizi Imatorbhebhe:
Sean, you had also asked about the kind of problems the innovation hubs may solve in the rare disease space. One of the challenges with rare diseases is that the natural history is very, very limited. We have very little information sometimes to go on because these diseases are so rare. One of the things that we are starting to see is this collaboration between various groups to share data. I mentioned earlier the FDA: they have the program called the Cures Accelerator Program, which they have done with various groups like CPAC and NORD, and through which they have agreed to share data, patient information data, making it easier to get better information about the patient's journey for that particular indication. We did this about a year ago, and it is helpful because, again, natural history is a challenge in the rare disease space.

From a clinical development point of view, one of the challenges that we face is being able to identify these patients: where are these patients located? How can we find them? Another challenge is being able to identify the sites or even physicians that treat these kinds of patients and that have the experience to do so. Our innovation center solves these types of issues. How do we leverage data? We leverage artificial intelligence, AI data, and data from all kinds of propriety sources to be able to pin-point where these patients are. We leverage genetic data with all the sequencing that has been going on. We also leverage data to identify who the treating physicians are, because quickly bringing these patients and physicians together creates a pathway to bring that drug to the market.

Therefore, from the industry's point of view, we make sure that we can find these patients - by leveraging various types of means from intelligence to genetic type data - and we make sure that we can find the physicians that have the right experience. We then marry them together so that the patients can get into these clinical trials, to hopefully bring these ready drugs to market quicker.

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Marshall Summar:
I had the privilege of being NORD's Board Chair for a while when we started the IAMRARE program, which was a natural history program. It has been a great success, I think there are over 50 Natural History registries going on now. We found that there are so many diseases and so many conditions, that trying to run, from the physician side, a natural history study out of an academic or even a non-profit environment, is really heavy after a while. However, the patient data is actually quite good. For instance, the registry program at NORD is part of the accelerator's program. That is patient-collected data: they can pull data in from physicians. It is a new way to look at how to build these natural history studies, because there are not enough patients to do cross-sectional analysis in rare disease. The only way to get enough data is to actually collect it over time. We found that the parents and the patients themselves are highly motivated to participate. I am seeing several pharmaceutical developments now using the data from those registries. In fact, the vision is that the natural history of a rare disease serves as the control, because, particularly with the more serious rare diseases, getting a family to enroll in a control arm is a very difficult and ethically challenging task. So I am very excited about the things going on. Thank you for bringing that up, Zizi.

Zizi Imatorbhebhe:
Absolutely. At ERGOMED, we are working with sponsors that are trying to bring these drugs to market, so we are seeing every day the huge challenges related to natural history that you described.

We briefly touched upon the ethical nature of this, which is another problem to overcome. We know that children are affected by half of the rare diseases, and that a third of children with rare diseases will die before their fifth birthday. So we are dealing with a lot of children and families – it is a family issue. In countries like the United States, for example, using children in control arms is seen as being a little bit unethical. So I think, like Marshall just mentioned, that having that natural history, using real world evidence, looking at ways we can use real world evidence and simple control arms, are other ways in which innovation hubs such as the one that we have, with NORD, the FDA, and some of the partners that we are working with, can help to solve this issue.

> ***"Having that natural history, using real world evidence, looking at ways we can use real world evidence and simple control arms, are other ways in which innovation hubs can help to solve this issue."***

Vinodh Narayanan:
Bringing us back to the challenges, just as an example: for many families, when their child has been diagnosed with a rare disease, we help to connect them with other families through Facebook pages. There is often no family support group existing at all. But when a small critical mass forms, they all seem to go through the same steps. The families get together, they launch a foundation, then they recruit a few scientists or clinicians, and they build a scientific advisory board. They have two goals: one is understanding the disease, and the other is developing treatments for the disease. I have seen this scenario happening repeatedly, whether it is a CHD2 Foundation or the Sinhgad Foundation. I think maybe Rare-X is a solution to this type of problem. It would be nice to have a solution eliminating this duplication of effort and whereby one global organization facilitates the development of patient registries.

Allowing for patients to be consented universally, while still having sub-groups within this global network, could create the right place for pharmaceutical companies and researchers to apply to use other cellular materials, patient materials, and to look for patients to recruit into small-scale clinical trials. Having a global clearing house would be wonderful to avoid doing the same thing over and over again for hundreds of diseases.

Marshall Summar:
That is one of NORD's missions, actually. NORD, for those of you who don't know, is the National Organization for Rare Disorders. There is also a CORD, the Canadian Organization for Rare Disorders - a very good organization. That is kind of the goal; NORD is an umbrella organization with 300 member groups. If you do the math, since 2000, the rate of new disease description or at least new linking of a genetic change to a phenotype is about 10 to 12 per week: it is definitely different from any other field of medicine in that regard. Concerning the rate of discovery: while we were having this conversation, there was a new disease found somewhere. To try to figure out how to do the research on those, how to move those forward, you have to share base precepts, concepts, and technique, so you don't reinvent the wheel every single time.

Sean Sanders *(host)*:
Ironically, we had Charlene Son Rigby from RARE-X on the last webinar that we did just a few weeks ago. I should have invited her back to this one. Anna, I wanted to give you a chance to jump in if you have any thoughts.

Anna Lehman:
I just wanted to build on what Zizi was talking about with the need for the real-world evidence. We can leverage our centers of excellence by having a better ability to track how new treatments are impacting patients and our healthcare system. We have a major issue in how to make our healthcare system sustainable with what is happening right now: an explosion of fantastic new treatments coming out for rare diseases that are tremendously expensive. These are being shown to be safe and efficacious, and are therefore getting marketing approvals through FDA and Health Canada. Our public insurance program has then to decide about coverage and coverage for whom. The data that was sufficient to show safety and efficacy is not always sufficient to show cost effectiveness to the degree that is really needed, as well as how total healthcare system utilization is being impacted. So again, I think the centers of excellence, by more robustly collecting information that is then being pooled from all the centers of excellence, are also going to help us with those really tough economic issues that are facing rare diseases, and increasingly so in the next five years.

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Marshall Summar:
I agree with you, Anna. I think innovation is one of the places we can address this. If you look at the cost of approval for a new rare disease drug, it is up to half of what a regular mainstream drug would cost - but then you have got a very small denominator underneath that. I think there are ways we can do this better. With the new gene therapies coming out, under our current model, it may be millions of dollars for one therapy. We must look at ways to leverage efficacy, durability, and similar things, into the pricing. I think innovation is actually going to play a role in the economics of this as well.

Sean Sanders *(host)*:
Thank you for bringing that up, Anna, it is not something that we talk much about, but the healthcare issue and health insurance is huge. It is sort of the elephant in the room. I am now interested in the role of advocacy groups in the centers of excellence and innovation hubs. Are they drivers or are they more marginalized?

Marshall Summar:
I think they are drivers. If you are working in a rare disease and you are not working with a patient advocacy group, you are missing the richness of data, but also on the people that will encourage you to keep going and the people that will bring patients together for either studies or

treatment protocols among other things. A lot of research in rare disease centers is often driven by the patient advocacy group. Families will come in and will say "We want work done on this." I think it is up to us in the field to make sure that we don't waste their resources and that we find productive ways to engage with them. They are absolutely at the center of it, and we would like more of that. What I am now seeing, as Vinodh mentioned, is individuals showing up saying, "Let's fix this or that disease." We do need to systematize the approaches more, both from the patients' side and the physicians' side, but they really are partners in this.

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Zizi Imatorbhebhe:
I agree. I think the patient advocacy groups are very powerful. Again, going back to something I previously said, it is really going to depend on the entity driving the center of excellence or the innovation hub. We have talked a lot about the FDA accelerator program. Well, that is done in conjunction with the patient advocacy group, NORD. They are big drivers in this.

Vinodh alluded to this earlier: when patients get diagnosed with a rare disease, they often feel alone. They feel they have been abandoned, they know that it is rare. So, one of the very first thing that they do is look for a patient advocacy group. The patient advocacy group, if there is one, becomes a conduit for them to learn more about what kind of treatments are available and what other patients or patient groups are in that particular area. They have a powerful voice. Here in the US, as many of you will remember with the Duchenne drug, for example, the drug was not initially approved. However, the patient advocacy had a truly powerful voice and was able to show that the drug benefited to their patients and their families in terms of quality of life. They were powerful in helping the FDA reverse a decision that would essentially have denied that drug.

Patient advocacy groups are also useful to us in our innovation center. For example, they can provide insights and input into protocols. How is this protocol being developed for patients in that particular indication? Is this protocol patient-friendly? Is it going to address and look at the endpoints that are important to the patient?

Sean, you also mentioned insurance and other such topics… There are many questions that need to be addressed. At the end of the day, to get the approval you need for the product, you want a protocol that is patient-friendly, but you also want a protocol that is going to eventually be peer friendly.

The advocacy groups are very important in the beginning stages in driving consideration for the protocols, identifying the patients for studies, for example, and in working with various groups to share data, patient registries, etcetera. They are also very powerful towards the end of the journey, when you are trying to get the drug out. If they are familiar with the drug and with its benefits, then they become very strong advocates for that drug, and eventually it is approved and sometimes uptaken by peers.

Marshall Summar:
I think, as you said, patient advocacy groups and payers make up a whole community that has to get involved with these. It is interesting to watch how the FDA responds. They have become very flexible around rare disease. As they have met with patient and family groups, they sometimes realize the urgency. So when we are looking at innovation and their engagement with the approval agencies, it has been quite productive in a number of studies that I have seen. I am curious to ask my fellow panelists, since we are talking about incorporating things like whole genome sequence, a lot of next generation data, phenotype… How do you see the role of machine learning advancing in the field of rare disease? There is a lot of buzz around it. It is very popular right now, but how do you see it playing out in the field of rare disease?

Vinodh Narayanan:
In the early days of our small center, we were using our own in-house developed software. The code was written by our own scientists. Back in 2011, we were using the first-generation Illumina machines. Since then, we have found that commercially available software packages are extremely up-to-date. All the latest data of all the databases where you might want to query are incorporated into these new software packages. They claim to include AI tools, probably mainly to predict splice variants: variants that you might predict to alter splicing of genes, and things like that. Another example for which AI tools are in great use is facial recognition, the FDNA software. Other than that, although we can set the rules through the software, we must manually analyze the data or the annotated files.

Zizi Imatorbhebhe:
That is a good point. We have seen AI used especially with facial phenotypical recognition in this space. Another way that we have seen AI used is to help speed up the diagnosis. One of the challenges in rare diseases is the time it takes to accurately diagnose a rare disease. We are seeing more and more uses of machine learning to help speed up diagnosis. As the majority of rare diseases are genetic in origin, speeding up diagnosis is a very important way to use AI, especially in genetic diseases.

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Anna Lehman:
I would just echo that, and frame it in terms of economics. As we incorporate more AI into the genomic testing process, the cost will come down if you would have to invest less human resources.

It is an expensive test or not depending on your perspective. The price needs to come down a bit for what I would like to happen, which is much more broad use of exome or whole genome diagnostic testing, especially in my field with adult-onset genetic disease. I see a lot of diagnoses that still take numerous years, because patients are just left to progress to quite a severe degree before someone finally says, "Okay, this looks like it could be a neuro degenerative condition". If the test was cheaper, then there could be a broader roll out. Also, decreasing the number of variants of uncertain significance decreases the downstream costs and part of the barrier of not wanting to order the test.

So, as we get more precise and a little bit cheaper, we can help more people.

Marshall Summar:
There is another factor which is labor shortages. We have a real labor shortage in the field in the States. On average, wait times for a clinical genetics program or a rare disease program can be a year or more for patients... In that cycle of trying to get to diagnosis, this can certainly push that way down the road. We are hoping is that with some of the new informatics tools, machine learning, AI, we can start to engage more of the mainstream physician core so that they can actually start the process. We may have to still be the ones, at the end of the day, that help to close it all out, but starting to move things further and further towards the primary care provider would be useful. I think I am starting to see that happen. We would like to see it happen in a way that makes sense for the patients. I think that is a huge area for innovation.

Sean Sanders *(host)*:
How do the primary care doctors interact with these centers of excellence and innovation hubs, particularly those working in remote areas? Canada has a huge swath where you have maybe one doctor for hundreds of people in a small village. How are they brought in when they are on the front lines? How can they feed into these hubs?

Marshall Summar:
We have always been playing with telemedicine in rare disease and medical genetics, but we weren't playing with it as seriously as we could. When we were suddenly forced to in early 2020, we learned that you can actually do a pretty good job. Sometimes there is no substitute for seeing a patient face-to-face, but there are a lot of things we can do remotely. Also, we can now get to patients that we couldn't reach before, either because of the distance from where we were, or from where the diagnostic center was. A patient who is more fragile shouldn't be traveling frequently. I work in a children's hospital – if you are a medically fragile patient, it is not always the best place to be from an infectious disease standpoint. We are working around a hub and spoke model. We have a collection of high-end specialists together, who then reach out to the community. The nice thing is that electrons are fast, so geography doesn't play an important role.

Also, some families face challenges to come in: they can't take a half day off from work, particularly some of our single working families. If we can see them at home or at school, we can actually do a lot better. We noticed a drop in admissions for some of our sickest patients, because we could see them faster and decrease that decision loop cycle around taking care of them. I would be curious to see if Anna or Vinodh have noticed the same thing.

Anna Lehman:
Because of the pandemic, our hospital launched a great Telehealth platform. We can now see patients who live remotely more often. Depending on what the patient's situation is, we might alternate between telehealth and flying down to Vancouver. For other patients, we might do all their appointments with us through Telehealth, and partner with a local physician to do a targeted physical exam that we send them as a sort of a "fill in the blank sheet". That has worked out well for other patients. It has been the one silver lining out of the pandemic that has transformed families' lives. It is so expensive to travel and to take time off work. I am really happy about that. Back to the first point, I am really looking forward to more neurologists, cardiologists, pediatricians, being able to order this genomic diagnostic sequencing to get faster diagnosis for patients as well. That can happen more locally as well.

Marshall Summar:
Yes, there is actually a lot of innovation going on around what I call "home evaluation kits", like EKG wearable devices that hook into your phone. It is going to be a real innovation field over the next few years. I don't think it will ever completely replace having the patient come in to be seen, but for many of our patients, it is much better than nothing at all.

Vinodh Narayanan:
Here in Arizona, the Native American Reservation is just up north of Phoenix. Again, access to healthcare is not always the best there. I think telemedicine has been a wonderful tool, but the first time you are seeing somebody, it does help to see the whole family, see the dynamics of the family, and watch the child carefully, because imagine a three-year-old in a room who may not be on camera, but may be running around all over the place… I think follow-up visits are very well accomplished by telemedicine, however, a telemedicine pre-evaluation to get a careful history from the parent is absolutely the best.

My colleagues and I have always been doing outreach clinics here in Arizona: we go once a month to Flagstaff, to the reservation at Chinle, or to Window Rock, to enable patients to have periodically access to specialty clinics. I think that the way to improve access to this technology for diagnosis is to have these kinds of mobile units or providers, maybe not a specialist, but somebody with an interest in rare disease, who would get on a bus or a van and drive out on a particular schedule and collect the information. Some of the information may already be collected by telemedicine, but it is very important to educate patients so that they don't think that they are being taken advantage of. The samples would then be brought back into the center of excellence for processing and sequencing.

Marshall Summar:
We found that with our patients with autism, telemedicine visits can sometimes be better. This is because bringing in a patient with autism to a new environment that may have sight, smells, and everything that are foreign to them, can actually be very disruptive. I recently had an experience with two twin brothers. The mother said "if I had brought him into your hospital, they would have destroyed the room and probably hit you several times". Instead, I was just talking to two young boys who were sitting there as calm as can be. I actually had a much better visit with them. So I think, like you said, that you must use it appropriately. It is not an answer for everything, but I do think it is a great force multiplier.

Zizi Imatorbhebhe:
I am sure that, with the pandemic, everyone has been hearing more about DCTs, decentralized clinical trials. Decentralized trials are essentially just trying to bring the patient closer to the study or to the site as opposed to having the patients coming to the site. In terms of incorporating technology, you see a lot of various technological aspects in DCT. We have talked about telemedicine. Some of you mentioned that many times, the patients still want to meet face to face. We find that most of these trials are not usually totally virtual, but rather take a hybrid nature, sometimes in person, sometimes from their home.

We also find that the innovation and decentralized trials also help with clinical trial diversity. Obviously, as you are aware of, there is a lack of diversity in our clinical trials. Because a lot of patients that are from underrepresented communities for example, they are not able to access

these clinical trials. I think having the innovative technologies, for example, does help with increasing diversity in patient trials, because these patients are now able to access the trials more readily.

You also talked about wearables: we have been seeing them quite a bit in industry. We have a number of wearables to measure various types of outcomes such as heart rates, etcetera, which can also be hooked up to the study. We also have the ability to send clinic nurses or home health groups straight to the homes, to supplement the work of the physician. I think the pandemic has been helpful in spurring on a lot of this innovation, technologies and decentralized trials. That has helped rare diseases, but it has also helped to increase diversity in trials.

Sean Sanders *(host)*:

We are coming to the end of our hour, but I wanted to ask one final question. We have talked about a lot of the positive sides of these innovation hubs. They seem to be doing really great things and there are a lot of advantages to them. My question is, how can they be improved? Is there anything that we are missing? Particularly, are there any unexpected benefits that might come out of the development of these innovation hubs that haven't been considered yet?

Zizi Imatorbhebhe:

Something we can look forward to is to answer the questions: how do we collaborate better? How do we share information? Anna, Vinodh and Marshall are all doing great work. How do all these groups talk to each other? How can they share the information? The idea of a center of excellence is to bring the best minds together. So I think one of the big takeaways is to understand the various differences in the different innovation centers, what they offer, and how we can collaborate and better share data, in order to help our rare disease patients.

Anna Lehman:

I think we need leadership at a high level to create the pathways for us to be able to share. Being a data steward is a lot of responsibility. The REBs sometimes struggle with figuring out what is safe, what is appropriate and how can one consents, re-consents and so forth over a very long-term horizon. Our governments and our organizational bodies should take a leadership role to create the mechanisms for this to happen. We need to link together, to be more organized and to collaborate more. That is my hope.

Vinodh Narayanan:

I have a suggestion from a private non-profit institution's standpoint. When I look through the list of centers for excellence in NORD, there are around 33 centers, all of which are major universities. They are not private non-profit groups like us. I would like to see a way in which it would be easier to include other organizations that are working in the rare disease arena to become partners. I have previously been on phone calls with the rare disease clinical research network mainly to see how we can learn from all the other centers to implement small-scale clinical trials with the handful of patients that we have at our center. For any disease, we might have one, five, or at most 10 patients in our center. However, there are a lot of administrative obstacles "Oh, you have to do this, you have to apply to this, wait until next year, the application opens up again". I would like to see opportunities for smaller places that are also working in the same arena to partner more easily with all the major centers, in order to contribute in some way, and to learn from them.

Marshall Summar:

Connectivity. I think the theme that we have all been discussing is that we need to share information and we need to share what we are doing. For example, for sickle cell anemia and cystic fibrosis, when people started sharing treatment protocols, there was an unexpected benefit. People start looking at what other people are doing and start adapting better practices. Many of the advances made in those fields are not so much from new drugs or new therapies, but are from using best practices and sharing those across. The Centers of Excellence Program that we launched at NORD last year was a patient resource enabling patients to find places that had a lot of depth and specialties. I think the next phase is connecting these. Vinodh, you have a really wonderful specialty organization. We need to get you connected to the Centers of Excellence Network. You should also think about becoming a NORD member. The key is getting a connection.

One thing I have also noticed in industry, is that once upon a time, when industry did a clinical trial, they held that data tightly - no one ever saw it, whether it was a positive or a negative study. I see now that industry is sharing that data. So instead of us having to go back and try to recollect it again - and with these small patient groups, you often can - that data is now becoming easier to share and is more cost-purpose. I am very optimistic about where things are going. I think we will see a lot of benefits just from the process of talking to each other.

Sean Sanders *(host)*:

Wonderful. Thank you once again to our fantastic panel and to Foundation Ipsen for enabling this conversation and the series through their kind sponsorship. Goodbye everyone.

Book # 12.10

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