A series of conversations
with experts on rare disease

# UNCOVERING RARE DISEASE

Volume 5

Webinars produced in collaboration with

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Have your say!

# Uncovering Rare Disease

Whilst rare diseases impact millions of patients, the journey that each patient undertakes for diagnosis and treatment is unique. Patients are spread across countries, languages, religions, races, economic brackets, and healthcare systems. Some patients in underserved populations have no access to rare disease expertise and need to travel hundreds of miles to get even the simplest diagnostic evaluation. Other patients may be discriminated against because of their appearance or handicap and so are stigmatized by society. Therapies may exist for some patients, but geographical and financial barriers stop the patients receiving the care they need. The struggles of people living with rare diseases are not just met by patients but also by those who care for them. For every patient with a rare disease, most of whom are children, there is a care giver. Caregivers may forgot quality of life, employment, and their savings to care for loved ones. Patients and their caregivers are often heroic; their challenges are great, exhausting, and heart-rending.

In this Science/AAAS Fondation Ipsen webinar series we examine the challenges faced by people living with rare diseases and examine some of the solutions needed to accelerate diagnosis, cure and care. Whilst some of these challenges will be met in the future, others are immediate. Stigmatization and discrimination against patients with rare diseases must stop!

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# Redefining Connection: How young people are shaping the future of the rare disease community through technology and innovation

In the age of digital connection, young people are building vibrant, supportive rare disease communities in ways that previous generations may not immediately recognize. Utilizing technology, social media, and innovative approaches, they are creating spaces for shared experiences, resources, scientific advancement, and advocacy that transcend geographical and generational barriers. These new forms of community are not only providing emotional support but are also driving research, awareness, funding, and policy change in the rare disease landscape. This panel will explore how young individuals are leveraging technology, digital platforms, and new methodologies to redefine what it means to connect, support, research, and advocate in the rare disease community.

Science Webinar participants will:

- Learn how innovative approaches are shaping the future of rare disease care and advocacy
- Explore the evolution of health care and research communities
- Engage with rare disease changemakers who are making their communities more inclusive, collaborative, and forward-thinking.

## Panelists

**Richard Horgan, M.B.A.**
**(Cure Rare Disease, Woodbridge, CT)**

**Yamina Hsaini**
**(Yamina's Life, Paris, France)**

**Pablo Ramirez Uribe, M.Ed.**
**(Rare disease advocate, Bethesda, MD)**

**Shandra Trantham, Ph.D.**
**(Rare disease advocate, Gainesville, FL)**

**Erika Gebel Berg, Ph.D.**
**(Science/AAAS, Washington, DC; moderator)**

## The Conversation

**Erika Berg (*host*):**
*Today we are exploring how young people are building vibrant and supportive rare disease communities in ways that previous generations may not have immediately recognized. Utilizing technology, social media, and other modern approaches, they are creating spaces for shared experiences, resources, scientific advancement, and advocacy that transcend geographical and generational barriers. These new forms of community are not only providing emotional support, but are also driving research, awareness, funding, and policy change in the rare disease landscape.*

*I would now like to take the opportunity to welcome our vibrant panel today.*

**Yamina Hsaini:**
My name is Yamina and I am from France. I suffer with severe gastroparesis and other conditions that are often misunderstood, so I felt lonely and faced medical mistreatment for many years. That is why I turned to social media and created "Yamina's life", where I share my life experiences to raise awareness, change mindsets, and break the stigma surrounding rare disease. Through my activism, I was honored by EURORDIS with the 2025 Social Media Award. I am here today because I believe in the power of using your voice to bring about change, and I am grateful to be a part of this important discussion.

***"I think that those of us who are able to tell our story should do so, and make sure that the stories of those who cannot are shared in some way."***

**Pablo Ramirez Uribe:**
I live with a condition called APS Type 1, or autoimmune polyglandular syndrome type 1. It is an ultra-rare condition, which affects one in every two to three million people. My genes really decided to take the whole rare disease thing to the nth degree. When I say that I live with it, I really do mean that in every sense of the word. First off, I am very lucky to even be alive, and luck truly played a big role. When I was three years old, a Colombian doctor happened to read a study on my condition that just matched up perfectly and I received proper treatment early on. My parents and my sister have basically given up everything to make sure that I have the best care. We have moved to different places, even to the United States, 15 years ago, to be right by the NIH. If the universe allows you to live and throws luck on your lap, you should in return give that back. I feel like there is a moral responsibility for those of us who have made it. So, from using my multilingual

background and working on writing to create nationally shared op-eds in Colombia, to learning at far too young an age (I was a very lonely child, I guess) how to use technology and social media, I created a YouTube channel and have been able to make some topics trend on Twitter. I also competed in speech and debate in college, where I gave a speech about rare diseases. And regardless of whether it led to being named one of Colombia's top 20 leaders of 2018, or being part of Rare Disease International's youth leadership program right now, more than anything, I keep going back to that living theme. Our Nobel Prize in literature winner, Gabriel García Márquez, called his autobiography, Vivir para Contarla, which translates to Live to Tell the Tale. I think that those of us who are able to tell our story should do so, and make sure that the stories of those who cannot are shared in some way.

**Shandra Trantham:**
I am a young adult in the rare disease community. I am living with Friedreich Ataxia, or FA. It is a rare neurodegenerative disease that I was diagnosed with when I was 12. I am a recent PhD graduate from the University of Florida, where I developed a gene replacement therapy for a very rare neurological disease. Being a patient and a researcher, I began to notice huge gaps in communication and became really passionate about bridging those worlds. I also learned in time that similar communication gaps exist between legislators and regulators, and patients and scientists. So I dedicated my time after school to learning all that I could to be able to actually do my part in breaking down those barriers. I am a proud ambassador of the Friedreich's Ataxia Research Alliance, and I am also a member of a young adult-only rare disease advocacy group called Young Adult Rare Representatives (YARR).

**Richard Horgan:**
I am the founder and CEO of a nonprofit biotech organization called Cure Rare Disease. We are advancing novel modalities to treat diseases of the muscle and brain. We are targeting diseases that larger pharmaceutical groups have traditionally left behind due to lack of prevalence, so the ultra-rare diseases, and figuring out a model by which the development of these therapeutics can one day become sustainable.

**Erika Berg (*host*):**
*I am going to put my first question to Shandra. Your work spans both scientific research and advocacy, which are two worlds that do not often intersect. How do you see young scientists like yourself using digital tools and social media to make science more accessible and connected to the patient communities that the science can hopefully someday benefit?*

***"It is important, as scientists, that we make every effort to share data and knowledge in layman's terms. I actually think that if you cannot explain something simply, then you probably do not fully understand it. It takes full understanding to actually be able to then put it into easier terms."***

**Shandra Trantham:**
As a patient myself, I think it is really important to emphasize that it is critical that we make scientific information accessible to everyone. I remember being 13 and trying to read about what was happening to my body in medical journals. Obviously, I was 13, so I had to look up every other word and it was really hard. That is why, as time has gone by and I have gotten older and learned more about science, I have used that knowledge to go back and help my patient community understand the latest news and research and things like that. Rare disease or not, we all want to understand what is happening to us. It is important, as scientists, that we make every effort to share data and knowledge in layman's terms. I actually think that if you cannot explain something simply, then you probably do not fully understand it. It takes full understanding to actually be able to then put it into easier terms.

As a scientist, I have been in plenty of spaces where others in the room had never met a patient with the disease that they were researching. It is kind of crazy. When I was in the lab, some of the people there were working on my disease and they had never met a patient before me. I have seen similar things happen with legislators. They have the power to make decisions that they do not personally know the implications of. So I have really come to realize how important it is for us as patients to share stories with these people to actually affect change. As scientists, we should really not be afraid to actually go into patient spaces, attend patient events, and things like that, so we can meet the people that we are trying to help and listen to their stories.

**Erika Berg (*host*):**
*Pablo, you talk about telling stories and you have used storytelling, YouTube, social media, and other channels to create impact across borders and across the globe. What role do you think language, culture and accessibility play in shaping inclusive rare disease communities online, and how can digital platforms do better in that space?*

***"I think all of us here are storytellers in that way, whether we are researchers, scientists, or advocates. Because of that, there are storytelling contours that all of us in the rare disease world can immediately relate to. A rare disease patient tells you about how a doctor did not believe them or how they were not accommodated at work or at school, and instantly, we understand. "***

**Pablo Ramirez Uribe:**
So, to preempt the response to that question, I am going to go off on something that may seem like a tangent, but to quote my friend William Shakespeare, "There is method to this madness." Because when we talk about storytelling, I am somebody who very deeply believes that we human beings think in stories. It is almost like a common language that we all understand instinctively. You hit us with a beginning, middle and end, and we follow you.

You tell us what somebody wants and the obstacles that they are going to face, and you have got yourself a plot that is going forward. And stories, honestly, can be anything. Richard Feynman, one of my absolute heroes, did an interview in which he talks about the process that makes fire, and not only does he frame it as this story, but he even gives carbon and oxygen desires, and I love that. I think all of us here are storytellers in that way, whether we are researchers, scientists, or advocates. Because of that, there are storytelling contours that all of us in the rare disease world can immediately relate to. A rare disease patient tells you about how a doctor did not believe them or how they were not accommodated at work or at school, and instantly, we understand. Similarly, somebody might tell you about their diagnostic odyssey, or how they feel they must live their life as a rare disease patient, caregiver or advocate to make sure that somebody with the condition that they are related to does not have to deal with so much later on. All these things are a common grammar that if we hear them, we relate to them in the rare disease world. So when it comes to writing in different languages, it is not as hard in that sense. For example, in Yamina's videos, she is able to put the subtitles in French and in English. Along with the videos, you instantly realize the visceral reality of what she is talking about, which I think you get in a lot of other examples.

In terms of culture and accessibility, we live in a time in which so much is available to us online, and not just for research purposes. In 2017, when I did that speech about rare diseases, I started by talking about Julia Vitarello, the mother of this beautiful six-year-old girl called Mila who had a condition called Batten disease. I learned just a few days ago that Richard has been working with the scientists who helped Julia develop the treatment for her daughter. I think it is called Milasen. Even though her daughter passed away, she was able to do this remarkable thing. So you go from researching a story in the Denver Post in 2017, to being at this event a few days ago and finding out that there is another connection, not just to the story itself, but to the person who played an integral role in it, and who is now related to Richard's cause as well.

***"The big thing for me is finding ways to support people in the rare disease community who have never been able to speak. With the technology we have nowadays we are able to do that, but how do we show them how to maximize the use of each platform?"***

I love what Shandra said about making information accessible to everyone. I think that is the great thing about the tools that we have now, but where do we go from there? Like you said, I believe that as we can rely on this common storytelling language and grammar, we can fit our stories within it and we can use the tools that we have around us. These may include visual tools, like YouTube, or image-based ones, like Instagram. You also have Twitter, Threads, and Bluesky to write small posts, or Medium and others to write longer ones. The big thing for me is finding ways to support people in the rare disease community who have never been able to speak. With the technology we have nowadays we are able to do that, but how do we show them how to maximize the use of each platform? How do we show them what YouTube can do versus TikTok, even though they are both video-based? How can we show them the fact that, as I have learned, Twitter is still used overwhelmingly in Colombia, so I use that one in Spanish a lot, but other ones like Bluesky and Threads are used more in English instead. How do we allow rare disease patients and others around them to realize that we have tools that can help them translate text, with nuance, into other languages? How can we let them know that they can look up videos, interviews, articles, and books, and that because of the multicultural world we live in, it is now much easier to relate to others regardless of cultural background? I think that if we approach it in that way, all the things we have, that are helping us create new senses of connection and community through shared resources and stories, can give people whose voices we have never heard before a chance to amplify them. Then we can come in and say, "All right, how do we show them what tools are available and how to use them in the best way?"

**Erika Berg (*host*):**

*Yamina, you have built a powerful platform rooted in your personal storytelling and your lived experience. What have you found to be the most effective ways to foster authentic connection online in a world of curated content? And how can digital spaces become safer and more empowering for young people with rare conditions?*

***"We can make digital spaces safer for young people by creating truly inclusive content. For example, we should focus on normalizing life with rare conditions and help others understand what it is like to live with them. By doing this, we create spaces where people are more likely to support one another. Because the more people understand, the less they judge."***

**Yamina Hsaini:**

I believe the best way to build an authentic connection online is by showing up exactly as we are, not as society expects us to be, but as our most honest version. For example, I share my daily life on social media, including my pain and vulnerable moments, but also my victories and my achievements, despite living with chronic illnesses. By opening up about my journey, people often tell me they can really relate to me. Speaking truthfully and sharing the challenges that I face helps create and maintain an authentic community, because people connect with what they can feel and with real stories. I think we can make digital spaces safer for young people by creating truly inclusive content. For example, we should focus on normalizing life with rare conditions and help others understand what it is like to live with them. By doing this, we create spaces where people are more likely to support one another. Because the more people understand, the less they judge. Step by step, we can create an environment where young people feel safe and can show up without fear.

**Erika Berg (*host*):**
*Richard, your journey with Cure Rare Disease is rooted in your personal story and has led to groundbreaking work in bespoke genetic therapies. How do you see young people and grassroots digital movements accelerating drug development and reshaping the future of rare disease research and biotechnology?*

**Richard Horgan:**
I think when we look at advocacy groups, non-profits, and family foundations, I would argue that it is not so much about accelerating certain groups of research, but rather about enabling them. So, for instance, of the more than 10,000 rare diseases impacting over 10% of the United States population, many of them are just far too rare to attract commercial drug development interests because there is no return on investment (ROI) on treating those diseases. That is not a judgment, it is really just an objective statement, with regard to how diseases are treated. These groups that you are seeing coalesce and bubble up to the surface, such as the work that Julia or others have done, or the work that we are doing, are trying to develop an approach that may be sufficient to develop therapeutics to treat these diseases. For instance, if you have a disease that affects only about 100 Americans, it is very unlikely to ever attract commercial drug development interests. However, in such cases our approach is to partner with academic groups that develop early stage versions of potential gene replacement therapies. Then our staff, comprised of translational experts, toxicologists, pharmacologists, and regulatory and manufacturing experts, take that early-stage drug and usher it through the development cycle, ultimately leading to an investigational new drug (IND) submission and the start of an initial clinical trial. Where we go from there is still the unanswered question. How do we take a drug that shows benefit, that may even be approved, and develop it so that it can be administered to patients who are impacted by the disease? I think that part remains unclear. From a technology perspective, we are in good shape. Can it get better? Absolutely. Will it get better? Undoubtedly. But can we treat certain diseases from a biological and physical standpoint? I would say that, for the most part, the tools and technologies to do so already exist to do exactly that. What lacks is the societal mechanism for funding and paying for this work. The funding component involves figuring out how to gather the millions of dollars necessary to take a drug from the initial academic bench all the way to the patient's bedside, and that is no easy task, especially nowadays. If there is a safety and efficacy profile that is acceptable to the regulators, which ultimately results in that drug being approved or perhaps even staying in perpetual IND, how do we ensure that patients can access that drug? These are the mechanisms that are unsolved today, but the way I like to think about it is at least we are not trying to change the laws of physics and biology. We are trying to modify the social fabric, and I would like to think that may be a little bit easier. The jury is still out. We will see, but that is where we are today.

**Erika Berg (*host*):**
*Cure Rare Disease is a nonprofit. Usually when you think about biopharma, a nonprofit is not necessarily what comes to mind. Could you expand on that a little and talk about how you operate and what it means to be a nonprofit in this space?*

***"If you looked maybe five or even ten years ago, the number of nonprofits driving drug development activities was effectively zero. Historically, nonprofits took the position of raising early dollars and then giving them to academia, or perhaps a small biotech, which would use them to develop a drug."***

**Richard Horgan:**
If you looked maybe five or even ten years ago, the number of nonprofits driving drug development activities was effectively zero. Historically, nonprofits took the position of raising early dollars and then giving them to academia, or perhaps a small biotech, which would use them to develop a drug. Until recently, nonprofits have not historically taken the lead and acted as the sponsor in developing drugs. Now fast forward to 2017 and 2018 with the advancement of efforts like Dr. Yu's work at Boston Children's Hospital, Dr. Neil Schneider's work at Columbia on rare forms of amyotrophic lateral sclerosis (ALS), and our work with the advancement of a personalized genome editor. Over the last five years, as these early-stage cases have come to the public's attention and have been published and discussed, they have opened up an opportunity for other groups that have historically not spearheaded drug development efforts to say, "Wait, actually we think we can do this."

So for us, as a nonprofit, there are very few, if any, investor dollars going towards funding the diseases that we work on, which is okay. How a lot of nonprofits function nowadays is through grassroots donations, NIH grants, state grants, and major philanthropic gifts. These, I would say, are unproven so far and are not sustainable. What becomes sustainable is how we can get drugs approved, reimbursed, and then reinvest those capital dollars back into new programs. So, it is a bit of a long-winded answer to your question, but I believe this new generation of decentralized drug development will especially benefit ultra-rare diseases that have historically been neglected and forgotten.

**Erika Berg (*host*):**
*Shandra, you were discussing earlier how you communicate research with the rare disease community. How does your lived experience impact that communication compared to a scientist working in that area without any? I was wondering if you could talk about that and what role technology or other types of platforms have played in that communication.*

***"I think technology has really helped the rare disease communities come together. We may be rare, but there are so many of us all around the world. Even though we all may have a different disease, we all share the same commonality of having a rare disease. We all share some similar struggles in getting people to understand our story and wanting to create meaningful change."***

**Shandra Trantham:**
Even as a scientist now, I can still remember what it was like when I did not understand everything. I was trying to understand, but it was honestly like hearing a foreign language and you do not know enough to even ask questions. I think that in order to effectively communicate, you have to put yourself in that position. Since I have been in that position in the past, I am able to think about what the news is and what I need to communicate and then how to frame it in a way that younger me would have understood. People in my community want to be informed, but do not know how to ask. So I think about all those things when I am trying to get information across. And it is not just speaking about information or writing about it, but you can also do things like videos that help share the impact or tying your personal stories into it so that people can better understand what you are speaking about and why it matters to pay attention. I think technology has really helped the rare disease communities come together. We may be rare, but there are so many of us all around the world. Even though we all may have a different disease, we all share the same commonality of having a rare disease. We all share some similar struggles in getting people to understand our story and wanting to create meaningful change.

I would say that I really began to notice the power of my own patient voice a few years ago when I came across this virtual education program for young adults in the U.S. that have a rare disease. It is called the YARR Leadership Academy and in this program, I met other patients like me who are using their stories to impact things like legislation, policy, and research funding. I formed a strong bond with my classmates who were there with me and who equally live with a rare disease. It is really empowering to use my voice to make a difference and to watch other young people use theirs. I do also want to echo what Richard was saying. I think that a lot of the problems that do exist are linked to money as it takes money to get treatments developed and approved. There are legislative mechanisms that help to bridge that gap and help push rare disease drug development forward. I think it is really important that programs like that continue to exist. I know that currently, one of these programs has not been renewed and is on pause. That could really impact rare disease program development and sharing our story can help bring that back and help create other methods of driving research and treatment development forward.

**Erika Berg (*host*):**
*What did you learn through your education program that might help others tell their story in order to reach a wider audience and make cases that regulators or legislative bodies might listen to?*

**Shandra Trantham:**
I would definitely say that the most important thing is tying your story to whatever you are saying so that people can really understand why it matters. The program that I was speaking about before, which has currently not been renewed, is the Pediatric Rare Disease Priority Review Voucher (PRV). This is a program that incentivizes rare disease drug development, because when a pharmaceutical company develops a treatment for a rare disease and if it makes it to FDA approval, they are granted a voucher. This does not cost the government any money, but the voucher is incredibly valuable because it actually allows for an accelerated review timeline for a drug, if you turn in this voucher. So companies will want to buy that for hundreds of millions of dollars. An example of using my story is that I have met with legislators, shared a little about this program, and explained that for a long time there were no treatments for my disease. While the fact that it takes so long to develop and review a drug through the FDA is, obviously, important for safety, as a patient it is hard to sit and wait for things to happen. Programs like this really incentivize companies to get involved in developing drugs for rare diseases, projects they might not otherwise pursue because they do not see a clear financial benefit to developing drugs for rare diseases with a limited patient population. So it is really important for this program to exist and I have met with legislators and shared my personal story to help better explain this so that people are able to have a better idea of why things like this matter. It can sound very complicated, but when you actually explain it in the context of your story it makes it a lot easier to understand and for people to see the impact.

**Erika Berg (*host*):**
*Pablo, you have had a huge impact using various strategies and I am wondering if you could talk about the ones you have found to be most effective for increasing awareness, sustained engagement and impact. What are some tricks we could learn?*

***"Figure out the answer to the question, "Why should they care about it?" Because unfortunately, simply saying they should care because it is human to care is often not enough."***

**Pablo Ramirez Uribe:**
I was actually talking about this with someone recently. We were in one of the groups from the Youth Leadership Program and we were talking about social media and the digital elements, and somebody asked, "I have only very recently started feeling comfortable sharing my story. How did each of you do it?" I basically said that I did it out of spite, and I will explain what I mean. I say this not about my immediate family, like my parents and my sister, but about other people in that orbit who would talk about the condition in whispers, as if it was some sort of taboo, yet also gossip about it. It still happens with one of my cousins. Her son also has a rare disease and I can see how these individuals behave in the same way. Very early on, I decided that I was going to talk about this at all times and that it was going to be out there in the public. I wanted to avoid the cognitive dissonance of people in my family being proud of me for who I was, because of course

they would talk about that, yet at the same time not want to talk about the rare disease that was a part of it, which would create a disconnect.

I love what Yamina said about showing people how things are and not how they expect them to be, so that the veil falls down and the reality is very present. I think the biggest tool that I have found is telling things as they are. Obviously within a level of not going to a dark place where you are destroying yourself to use your own personal story and not practicing self-care, but ask yourself what are the things that you think need to be out there so that people care? As Richard mentioned, when we are talking about different conditions and you want to convince people to care about them, it is not an easy thing to do. For example, with a medication that is only for a few hundred people. As an English teacher, I would tell my students when we write persuasive essays that you need to have a "So what?" question. Tell me why I should care about the topic you are writing about. Does it connect to me personally? Is it going to affect the economy in some way? Is it going to affect future generations? And when you find that little through line that will reach a different audience member, you have succeeded. That is how you get them to understand that it actually does impact them and they want to learn more. I feel like I am still stumbling backwards into using social media and writing narratives, but there is always something new that you learn when testing things out. I would suggest that you find a way to boil down one part of your story to the basic essentials: beginning, middle, and end. Ask yourself what do you need right now? What is blocking you? Choose one avenue or one audience, whether you are a middle school or high school student talking to your classmates to celebrate Rare Disease Day, or you are a researcher or executive wanting to see if you can reach your audience. Figure out the answer to the question, "Why should they care about it?" Because unfortunately, simply saying they should care because it is human to care is often not enough.

So, find that, "So what?" which is very specific to them, and then just test out different methods. If nothing else, they are changing so fast that I think a lot of us might not even know in a few years from now what the tools are that work for some of these platforms. So if we at least start working now, while being afraid of failing and making mistakes (which is good, because it means that it is important work and we care about it), as technologies develop and the landscape of the rare disease world changes, we will already have some experience. This way, we can adapt as opposed to starting from scratch and having to learn how to do something while also navigating the rare disease world. In conclusion, I would say: find that "So what?", learn how to tell your story, and test out different strategies, because things are changing so fast and we will be the trailblazers.

**Erika Berg (*host*):**

*Are any of you using artificial intelligence (AI) to help tell your story or in creating those connections?*

**Pablo Ramirez Uribe:**

I am an early adopter of all types of technology, and as an English teacher who knew that students were going to start using it to write their own essays, I remember just going for it and trying it out. I tried 30 or 40 different prompts from "write a five-paragraph essay" to "write a passive-aggressive email", which I sent to two of my colleagues, who are also my best friends. I was trying all these different things to see how this tool works and to understand its limits. Bless the heart of my students, they thought I was born yesterday and we would not catch it, but there are obvious things that artificial intelligence and generative AI cannot do. So what could it do? It could take the text or the transcript from a YouTube video in another language and translate it for us, and then that is where we add our little bit of flavor and nuance. It can help, as I know a lot of researchers are doing, with collating data about different symptoms and seeing what they reveal. I met somebody at the World Orphan Drug Congress recently who is trying to collect data for different conditions using established registries. They are using registries to collate all that data and see what symptoms are mentioned most often. That way, whenever physicians test for something, the model can use what it has already learned to support the diagnosis. We can see how effective it is at using the information it takes in to potentially diagnose someone sooner rather than later. It is a very exciting and, at the same time, terrifying tool, and I can see so much potential for it in the rare disease world.

**Erika Berg (*host*):**

*Anyone have anything to add from the research side?*

**Richard Horgan:**

We do use AI in a slightly different sense. We are using AI to optimize the sequences of the drugs we are developing. There are known areas where certain DNA sequences, made up of the nucleotides A, T, C, and G, elicit an immune response. What we do is we feed our sequences into an AI machine learning platform, and then that is able to generate what we call optimized sequences that are less likely to elicit an immune response. In the case of the drugs we are developing, they are delivered with a virus, called adeno-associated virus (AAV), which is an immunogenic virus. Clinically, patients have their immune systems suppressed and T and B cells interrupted so as not to elicit an immune response. In leveraging AI, our hope is that we can further improve safety. So it is very novel. The jury is still out on its efficacy, but we will see.

**Erika Berg (*host*):**

*Yamina, you have a deeply personal and honest social media presence. Can you share with us your biggest challenge and your greatest reward in digital storytelling? And how do you keep your community grounded in a sense of hope and resilience in something that can sometimes have dark aspects?*

> ***"Even when there were negative people, it never stopped me from advocating because it only reminded me of how important it is to change the way people think. My biggest reward is the community I have built and the safe space I have created, and the way I have turned my pain into my strength."***

**Yamina Hsaini:**
My biggest challenge has been exposing my personal life while raising awareness about illnesses. This is because it means opening up completely to a large audience, knowing that I am talking about complex and often misunderstood topics that many people have never heard of, which can often lead to confusion or judgment. Even when there were negative people, it never stopped me from advocating because it only reminded me of how important it is to change the way people think. My biggest reward is the community I have built and the safe space I have created, and the way I have turned my pain into my strength. When all the medical injustice started in my life, I did not know anyone going through something similar, but by sharing my experiences, I help others avoid the same loneliness by giving them the kind of hope I wish I had back then. I have inspired many people to accept themselves and fight to be understood. All of this keeps my community grounded in hope and resilience by accepting the struggle and growing through it together with truth and support.

**Erika Berg (*host*):**
*Shandra, we often hear about the isolating nature of rare disease. How has technology helped you feel less alone and can you talk about any meaningful connections you have built through digital spaces?*

**Shandra Trantham:**
I can really speak to this one.  As I mentioned, I was diagnosed with FA when I was 12. At the time, I was in middle school, and obviously, I was very ashamed of being different from other people. I actually did not even tell anyone about my diagnosis until I was in college. The symptoms were obvious to other people, but I always just played it off as some other excuse, and I was really afraid to tell people what was really going on. In college, I finally started to tell some people around me that I was really good friends with, and their response of being okay with my big secret made me feel better about reaching out to other people with FA. Obviously, with it being a rare disease, I did that online. That has really changed my life and the trajectory of everything that I am doing. I joined something called the Patient Ambassador Program at the Friedreich's Ataxia Research Alliance. In that program, we meet monthly and there are usually about 50 people with FA on the call, coming from all across the country and the world. We meet monthly to connect with each other, learn new things that are going on, and find ways that we can help make a difference.

Through connecting in the Ambassador Program, I have met some of my best friends that I am very close with now. I actually lived with another person with FA. He is my best friend, and we lived together for two years, and now we are neighbors. So, it has really made a difference. Being able to connect online when you have a rare disease means you are actually able to have a community, which you may not have had otherwise due to geographic limitations.

***"Technology, especially social media, became the only place where I could stay connected and finally feel less alone by finding people who understand me. I just had to log in to share things I used to keep to myself. Suddenly I felt surrounded."***

**Yamina Hsaini:**
Personally, I was isolated at a time in my life when most young people are building a social life. Technology, especially social media, became the only place where I could stay connected and finally feel less alone by finding people who understand me. I just had to log in to share things I used to keep to myself. Suddenly I felt surrounded. The most meaningful connections I have built were the people who supported me like I was someone close. For example, when I could not afford treatment, they helped me. When I shared my struggles, they offered solutions, advice and care. For me, digital spaces have become much more than a virtual place. They are where I found support and connection, and they literally saved my life.

**Erika Berg (*host*):**
*Richard, I wanted to ask you about access, as the money question keeps coming up. How can we help to reduce these disparities in access and make sure that technology does not increase those gaps rather than shrink them? We are developing these amazing new research technologies, but how do we make sure that people can still access those tools?*

***"Simplifying the reimbursement process for these ultra-rare diseases, which have limited (if any) commercial opportunities, could greatly improve accessibility."***

**Richard Horgan:**
I think there are a couple ways. The first is the point Shandra made about the PRV. I think for the work that we do, it is essential. It is not something that is costing the taxpayers millions of dollars. These are secondary market transactions that are not putting a huge burden on the American taxpayer, but they are hugely catalytic. I think the second way is with regard to improved flexibility within regulatory decision-making and policy. We have talked to state plans, federal plans and CEOs of private plans to get a good understanding of how they all think about paying for drugs. The short answer is that drugs are paid for once they have achieved commercial approval. This is done by obtaining a Biologics License Application (BLA) or a New Drug Application (NDA) after having gone through clinical trials. So those two things are generally joined at the hip.

For ultra-rare populations, we are never going to be in a universe where we can have 100 or 200 patients in a study; by the nature of ultra rare diseases, that will not happen. However, I strongly believe that with regard to increased flexibility within regulatory approvals, if we can show meaningful benefit against some sort of established baseline, whether the individual is their own control or there is a natural history study published for a disease, we could potentially see the commercial approval of a drug on the back of two, three, or four clinical trial patients. This may sound somewhat new, but when we are dealing with populations that are 30 to 50 patients, treating 10 to 25% of the population is meaningful. Such data should be sufficient to signal whether the drug is effective and whether it is safe. This has to be partnered with long-term follow-up, as it cannot only be a one year period and then it is over. We need to have that post-market surveillance activity going on. So I think that increased flexibility in drug approvals then allows insurance to pay for those drugs, which in turn improves accessibility. Around half of Duchenne muscular dystrophy patients do have Medicaid as well as private insurance, in some cases. Simplifying the reimbursement process for these ultra-rare diseases, which have limited (if any) commercial opportunities, could greatly improve accessibility. This, paired with the PRV, offers us the incentive to get this work done on a smaller scale. I think the challenge with traditional drug investment, from a venture perspective, is that we are looking for a one to 100-fold return on our investment. I would encourage venture groups to look at this differently: if we can create a framework where a drug for 20 people can get a commercial approval on the back of a clinical trial of two, three, or four patients, then we can make a larger number of smaller bets, and still achieve returns of 100 times our investment. The returns are just spread over a larger portfolio.

**Erika Berg (*host*):**

*Looking ahead, what do you think the rare disease community will look like 10 years from now? What are you most excited about and how do you hope that you could potentially contribute to that vision?*

**Pablo Ramirez Uribe:**

I was racking my brain trying to figure out what I think it is going to look like. While I cannot really answer that question, I think that we will have more people alive and connected. I think we will have a lot more family members that will see that person live and flourish, whether it is through researching treatments or the conditions themselves, or being able to share that message and speak our truth to the world. Hearing from everyone is the most exciting part and I feel very lucky. You do not choose to be born into this world, but we are in a moment in which I can say to myself, "I am very lucky to be able to share spaces like these." All I know is that I am excited because there is going to be a lot of work that needs to be done. But man, it is going to be incredibly fulfilling 10 years from now.

**Yamina Hsaini:**

I think in 10 years, the rare disease community will be a space where young people with chronic and rare conditions feel included from the beginning, not after years of silence or medical injustice. I hope to contribute to that future by continuing to raise awareness through storytelling and by creating new kinds of spaces to share my experience.

**Richard Horgan:**

I think the next decade of rare disease achievements will pragmatically look like more safe and effective drugs on the market and an ability to pay for them. Over the next few years, with these three or four million dollar gene therapies, we will see how that works. I anticipate seeing an increase in value-based reimbursement. We cannot just dole out four million dollars for a drug that may or may not work for every patient. But we will see. I think it is up to conversations like these and groups, in a broader sense, to keep pushing that edge forward into the great unknown. I am hoping for the best.

***"I would love to see people with rare diseases working not only in science, but also in the government and at institutions like the FDA, so that our voices can be heard on a larger scale."***

**Shandra Trantham:**

I think the future is going to look like a lot more patients with rare diseases in these spaces where we previously had no presence. I am now a scientist with a rare disease and my best friend, who I mentioned earlier, was also in my graduate program. So that makes two of us in science at this one school who have a rare disease (that I know of). I have also been hearing about lots of other people that I have connected with online that are in science and have rare diseases. I think that is really great. I hope that we will continue to occupy other spaces too. I would love to see people with rare diseases working not only in science, but also in the government and at institutions like the FDA, so that our voices can be heard on a larger scale.

## Bridging silos: How scientists studying rare disease are building cross-disease communities to advance research and innovation

In the realm of rare disease research, collaboration across disciplines, organization types, and disease types is essential to accelerating progress. Traditionally, scientists have focused on studying individual rare diseases within their specific silos, but as the understanding of genetic, molecular, and therapeutic commonalities across diseases deepens, researchers are increasingly looking to connect and share insights with those studying different rare conditions. By forming cross-disease communities, scientists can foster new ideas, discover shared mechanisms, and catalyze innovative treatments that might otherwise remain isolated within the boundaries of a single disease focus. This panel will explore how scientists are overcoming the challenges of working in rare disease research, how they're using platforms, technologies, and other community-building strategies to collaborate across disease areas, and the unique benefits that arise from interdisciplinary cooperation. By sharing resources, knowledge, and expertise, scientists are building a collective force that drives more impactful research and quicker advancements toward new treatments.

Participants will:

- Understand how cross-disease collaboration accelerates rare disease research and innovation
- Identify tools and strategies that support interdisciplinary research communities
- Recognize common challenges and solutions in building cross-disease collaborations.

## Panelists

**Julian Beach, M.B.A**
**Medicines and Healthcare products Regulatory Agency (MHRA), London, England**

**Stephanie Cherqui, Ph.D.**
**University of California San Diego, San Diego, California**

**Daria Julkowska, M.A.**
**European Rare Disease Research Alliance (ERDERA), Paris, France**

**Kerry Jo Lee , M.D.**
**U.S. Food & Drug Administration, Washington D.C.**

**Erika Gebel Berg, Ph.D.**
**Science/AAAS, Washington, DC; moderator**

## The Conversation

**Erica Berg (*host*):**
*Today we will explore how collaboration across disciplines, organization types, and disease types is accelerating progress in rare disease research. By forming cross-disease communities, scientists can foster new ideas, discover shared mechanisms, and catalyze innovative treatments that might otherwise remain isolated within the boundaries of a single disease focus. This panel will dive into smart strategies in research and policy that are helping scientists studying rare disease become a collective force that drives more impactful research and quicker advancements toward new treatments. I would now like to take the opportunity to welcome a truly distinguished panel.*

**Kerry Jo Lee:**
My name is Dr. Kerry Jo Lee. I am a pediatric gastroenterologist and hepatologist, and I serve as the Associate Director for Rare Diseases and the lead for the Accelerating Rare Disease Cures Program at the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

**Daria Julkowska:**
My name is Daria Julkowska and I am the Assistant Director of the Thematic Institute of Genetics, Genomics and Bioinformatics at INSERM in France. I am also the coordinator of the European Rare Diseases Research Alliance (ERDERA) which is the largest rare disease partnership in Europe.

**Stephanie Cherqui:**
I am Stephanie Cherqui and I am a professor at the University of California San Diego (USCD) in the pediatric department. My lab focuses on developing a new therapy for rare diseases using hematopoietic stem cell and gene therapy, and we take research from bench to bedside. I am also the director of a gene therapy initiative at UCSD.

**Julian Beach:**
I am Julian Beach and I am the Interim Executive Director for Healthcare Quality and Access at the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. In my role, I lead medicines licensing within the UK for all medicine types, from innovative to established medicines. It is really great to have this conversation about rare disease therapies and how we can accelerate their use and take-up.

**Erica Berg (*host*):**
*I am going to put the first question to Kerry Jo. We have been talking about cross-disease collaboration or taking rare dis-*

*eases as a collective in order to try to make progress. What are the biggest benefits you have seen from cross-disease or interdisciplinary collaboration in rare disease research and can you share a concrete example?*

> ***"There are complex challenges in developing rare disease therapeutics that not only benefit from, but need, the multiple perspectives from all members of the community."***

**Kerry Jo Lee:**
From the perspective of developing and delivering rare disease therapies to patients that are safe and effective, rare disease drug development really takes all members of the community in order to be successful. Patients, academics, clinicians, industry, and regulators all have to work together. There are complex challenges in developing rare disease therapeutics that not only benefit from, but need, the multiple perspectives from all members of the community. These insights help inform optimal clinical trial design, establish fit-for-purpose endpoints for rare disease clinical trials, and enhance our understanding of the therapeutic landscape of benefit-risk from diverse patient populations. Silos are simply not effective when you are trying to move the needle and avoid reinventing the wheel over 10,000 times for 10,000 various rare diseases. We have many examples at the FDA where research has aided therapeutic development, particularly in the pre-competitive space. This is where it really helps us inform novel approaches to innovative clinical trial design, looking at the use of Bayesian methods and smart designs to reduce the numbers of patients you would need to have in various arms of clinical trials. We have been characterizing fit-for-purpose endpoints, such as novel surrogate biomarkers or clinical outcome assessments, both of which are critical to incorporate into a clinical trial. Our therapeutic product centers engage in public-private partnerships, consortia, workshops, and work with researchers through grants that are administered to define, for example, the natural history of patient populations, in coordination with our Office of Orphan Products Development or through the FDA's Broad Agency Announcements. So there are many different ways in which we work with the community in order to foster the advancement of science.

**Julian Beach:**
I think it is the cross-disease registries. It is the patient registries. It is using the data, because one of the critical aspects for me is that rare diseases, by their definition, are rare. So it is how you can bring together enough information to make a common pathway or how you can make pools of data big enough to actually reach a critical mass. This then allows you to look at what is possible from a regulatory point of view or what makes sense from a scientific point of view. But ultimately, how do you then consider each patient's data individually and use it to treat them? I think there is a number of ways, but it is really about seeing how you can pool data to then look at how to treat that individual.

**Stephanie Cherqui:**
If I can add on that, pooling the disease data together and delivering the technology, as Kerry said, is very important. You asked for a concrete example. There is a nonprofit organization called n-Lorem that stands for Nano-Rare Patient Colloquium. It was created by an expert in antisense oligonucleotides (ASOs). They created this nonprofit organization to be able to use the same ASO technology for extremely rare diseases. Sometimes it is an N=1 patient population. But because the technology is shared across all these diseases that meet certain criteria, they can treat these patients for life. I think this is a beautiful example of how collaboration between experts and physicians, who are ready to give their time to deliver this new technology, can really impact patients with an ultra rare disease.

**Daria Julkowska:**
If I may add a final comment, from a different perspective. For me, this interdisciplinary and multi-stakeholder collaboration is something that led to the creation of the European Rare Disease Research Alliance, which we call ERDERA. We went from having only 20 different funding bodies in 2015 to more than 180 organizations today, which encompass funders, industry, patient organizations, research performing organizations, hospitals, and infrastructures that really work under one umbrella to accelerate the rare diseases ecosystem. So there are different dimensions and I think this kind of structural dimension is also very important.

**Erica Berg (*host*):**
*I have a follow up question for you, Daria. ERDERA is bringing together stakeholders from many different countries. What has surprised you the most in terms of what makes these types of cross-border and cross-disease collaborations successful or challenging?*

**Daria Julkowska:**
Today we have 37 different countries participating in ERDERA, so as you can imagine, it really goes beyond Europe. We also have Canada, Australia, and New Zealand, for example, on board. What surprises me is that we release a lot of funding opportunities and what we have noticed is that bringing the different consortia together is already sufficient to foster collaboration. First of all, many of them are being built from scratch. We often say that the rare disease community is small and we would think that everyone already interacts a lot and everybody knows each other. But in reality, when it comes to the research projects, there are a lot of consortia that are gathering new resources and complementarities together. And even if, in the end, those projects are not selected, it is already enough to sustain the collaboration. So I think this was one of the most surprising things, because it means that the collaboration is so important that even though they do not receive support from funding, they still continue to collaborate. When it comes to more difficult aspects, sometimes it may be the language barriers, but most of the time it is something outside of the research problematic.

We had this experience where we financed clinical trials in which we had groups from multiple countries and every time they needed to revise the protocol, it had to be translated into all the nation-

al languages, which led to additional delays or costs for the trial. So there are some things that are outside of the research scope or research parameters, but they may hamper or at least delay the collaboration.

**Erica Berg (*host*):**

*Julian, I was wondering if you could share some common scientific or therapeutic themes that you have seen emerge across different rare diseases that make this type of cross-disease research so valuable?*

**Julian Beach:**

I think there are a number, but it is all about identifying where there are underlying genetic mutations or where there are treatments that could target common pathways. Are there particular targeted therapies that could work across different disease areas or different condition types? I think it is really about looking at the different effective therapies, which can be based on very different technologies. These might involve delivering a payload, accessing mRNA, or using CRISPR, to apply targeted-type aspects based on genomic sequences. In the future we may potentially sequence a person's germline to help determine which therapy would be most effective, so the therapy is personalized to that individual. All of those things will then enable that research base to come up with those final therapies. I guess this is also where we use this kind of research to inform other research, which then can be applied to broader areas of medicine and larger populations of thousands or ten thousands of people. So there are translatable elements and the focus on rare diseases really drives that research. It drives thinking. It shifts the paradigm and challenges us to reconsider how we think about medical research. So with the human body, when you have the genomics to understand what tests can be put in place and what different diagnostic tools that you would then need to develop, all of those aspects can then be translatable across different disease types to give you that final outcome.

> ***"Natural history studies and understanding the natural course of a disease are very important to help plan and develop a trial that is going to demonstrate substantial evidence of effectiveness or characterize safety."***

**Kerry Jo Lee:**

To build upon what Julian was talking about, translational science is a critically important area for rare disease drug development. The translational science, particularly within CDER for the therapies that we have, helps to support the selection of novel surrogate biomarkers, which is very important when it takes too long to see the effect of a clinical outcome. Translational science also supports what we call confirmatory evidence. Mechanistic and pharmacodynamic data can comprise the confirmatory evidence, which is the part of a marketing application that helps to demonstrate substantial evidence of effectiveness, in addition to the one adequate and well-controlled trial that is conducted. Those are really critical aspects of translational science that help to support how we think about putting together and reviewing marketing applications for rare disease therapies. There are two other components of research that are also very important. We support a lot of research on natural history studies. Natural history studies and understanding the natural course of a disease are very important to help plan and develop a trial that is going to demonstrate substantial evidence of effectiveness or characterize safety.

We have a lot of heterogeneous patient populations due to phenotypic and genotypic diversity. Understanding what those subsets are, even within a rare condition, can help you pick the right patient population for your therapy, the right trial duration so that you can demonstrate an effect, and can also help you pick the endpoints as well as the timing of those endpoints in order to demonstrate an effect. So natural history study is one component. Finally, we have support for statistical innovations and modeling that really help us find new approaches that might be successful, that lead to benchmarks for how we interpret the success of studies. So all of those are different ways in which I think we support research as well.

**Erica Berg (*host*):**

*Stephanie, I want to talk about your research, which spans a spectrum of diseases, from cystinosis to Alzheimer's disease. What insights or techniques have translated unexpectedly well across these very different diseases?*

**Stephanie Cherqui:**

Cystinosis is a very rare disease that affects perhaps 3,000 to 4,000 patients in the world. I was always passionate about gene therapy, and at the time I was involved in finding the gene responsible for cystinosis. When I had to develop the gene therapy approach, we realized that it was a very challenging disease because all of the organs are degenerating, so we have to bring a new protein to all of the organs. The protein involved is non-secreted, so it was very hard to provide this protein to all tissue cells. However, I was already involved with the families and the community, so I really wanted to make a difference. I decided to use bone marrow stem cells, and in particular hematopoietic stem cells, to try to deliver this protein to all the tissues as these cells can naturally migrate and engraft in all the tissues throughout the body. Very unexpectedly, the hematopoietic stem cells had a very dramatic positive impact on the disease in the mouse model. We were able to then go from the bench to the bedside. We have now completed the phase one and phase two clinical trials with positive outcomes. This program has now been acquired by Novartis and we are going to start the new phase of the trial.

Along the way, we asked ourselves, "How can hematopoietic stem cells, which give rise to blood cells, generate this tissue rescue throughout the body?" We determined the mechanism of action and realized that we could create macrophages or microglial cells in the brain, which then form tunneling nanotubes to deliver the organelles to diseased cells. This discovery led us to ask, "If this works for cystinosis, why can it not work for many other disorders that involve non-secreted proteins that are found in organelles?" From there, we have now been able to apply the same technology to Danon disease, which often requires patients to undergo a heart transplantation, Sanfilippo syndrome type C, which

is a neurodegenerative disease, and also Friedreich ataxia, which is a mitochondrial disease. So this has opened a completely new way of treating these patients. We will also be starting a clinical trial next year on genetically modified hematopoietic stem cells. What we learned from each disease has revealed so much about the mechanisms of action and their potential for use in the central nervous system. We thought why not apply this approach to Alzheimer's disease? There were clues that suggested it might work, and, indeed, in the mouse model, we were able to rescue Alzheimer disease with the same technology. Now we are also working towards translating these findings into clinical applications.

***"That is also the message I give to my students, each time I have the opportunity to do so: please work on a rare disease, because whatever we learn can be applied to so many other diseases. There are more than 400 million people out there with a rare disease, and so few have an effective treatment. We can learn so much and apply these findings to so many other diseases."***

I remember during my PhD, one of my committee members saying, "You have done a great job finding the gene for cystinosis and making the mouse model, but why do you choose to work on such a rare disease?" I answered him by saying, "First of all, there is no rare disease when you are a parent and your child is affected by a rare disease." Thank God there are people who work on rare diseases. I also told him, "What you learn when studying a rare disease, you can apply to so many other disorders." I wish he could see me now, because this is exactly what happened. That is also the message I give to my students, each time I have the opportunity to do so: please work on a rare disease, because whatever we learn can be applied to so many other diseases. There are more than 400 million people out there with a rare disease, and so few have an effective treatment. We can learn so much and apply these findings to so many other diseases.

**Erica Berg (*host*):**

*I think we have done a great job of making the case for why this type of cross-disease collaboration is so important in the rare disease space. I am now going to shift gears a little, to talk about how we build and sustain these collaborative communities of researchers, regulators, and all the other stakeholders, that make progress faster and better. Daria, how do you build trust and a shared language among researchers, clinicians, regulators, industry, and patient groups, who may come from very different backgrounds, in order to work toward a common goal?*

***"We soon realized that that a neutral mediator, who was able to facilitate the dialogue between the industry partners and the academics, was essential."***

**Daria Julkowska:**

I would say it requires mediation, mentoring, and training. Why do I say that? Because we cannot expect every stakeholder to fully understand each other's perspective from the start. We have a lot of experience in building a full pipeline for these collaborations. For example, in our public-private partnerships, such as the Rare Disease Research Challenges, we have seen it play out. In these initiatives, industry partners, in collaboration with patients, have set challenges to which academics have responded with proposals. We soon realized that a neutral mediator, who was able to facilitate the dialogue between the industry partners and the academics, was essential. This is because there can often be a preconception or misinterpretation of what the other one is like. The industry might be seen as always wanting to make money, while academia may be perceived as not always delivering the high-quality or usable outputs, for example. So this is something that we have learned and we are applying. We also offer free mentoring services to research applicants. When the consortia apply with the research projects and are invited to submit their full proposal, they have the possibility to access a pool of mentoring experts that are specialized in quality assurance, statistics, innovative methodologies, regulatory affairs or business development. They can accompany the consortium in a way that helps them better conceptualize their project, ensure follow-up, and work towards concrete outputs. The final aspect involves the dialogue and understanding between patients and research communities. We have realized that setting up dedicated workshops or trainings where researchers and patients are sitting together, to better explain what they do and what their needs are, can be really successful. Currently, for our funded projects, these kinds of trainings are mandatory before they start the project. It is in this way that we can ensure that we apply different types of tools, without putting the burden on the research groups, patients or other stakeholders, so that they have all the knowledge from the start.

**Julian Beach:**

I think it begins with building a foundation of communication. One of the things that the MHRA does very well is having that open communication style, and I think that really goes a long way. As Daria was saying, the easier you can make communication, the more scientific conversations you can have and the more language is deconstructed so that you do not build artificial barriers. Something that I see quite regularly is that there is a fear factor. People think, "Should I have a conversation? Should I do this? Should I do that? Should I talk to a regulator? Should I talk to a funder?" We really need to ask how we can help and support people as they move through their careers and experiences so that they can focus on that patient outcome and bring the patient perspective into the conversation, and stay centered on what the ultimate aim is. So it comes back to a basic level of communication and trust. How do you generate human relationships? How do you have that overall discussion to reach the desired outcome?

***"We also have very robust programs in patient-focused drug development as well as patient listening sessions where those communities can come and talk to us and share their lived experience so that we understand the risk-benefit considerations and what it is like to live with a certain condition."***

**Kerry Jo Lee:**
I wanted to add just a few more things on this topic, because I think it is a really critical aspect of how we are going to succeed moving forward. I wholeheartedly agree that it is through engagement, but also through education. We often hear at the FDA that we are a black box and people do not understand how we work or the regulatory components of how to move from bench to bedside. So we definitely have been strong proponents of engagement through our public-private partnerships, consortia, symposia, and public workshops. We also have very robust programs in patient-focused drug development as well as patient listening sessions where those communities can come and talk to us and share their lived experience so that we understand the risk-benefit considerations and what it is like to live with a certain condition. This is very valuable to how we think about advising on the clinical trials that are submitted to us. Finally, the education component comes with an access aspect. We have a history of putting on these workshops at the FDA that were in situ: they happened in a moment of time, and if you were there, you got the lessons, but it is hard to find them afterwards. One of the things we have tried to do through the Accelerating Rare Disease Cures Program is list those that we think are really impactful for rare disease drug development on our website. That way stakeholders can simply use the dropdown menu to look at the components such as how we use real-world data, what the innovative statistical designs are, how to collaborate on natural history studies and registries and why they are so important, and have all that information available to access whenever they need it.

**Erica Berg (*host*):**
*Stephanie, can you talk about your role in research consortia, such as the Cystinosis Stem Cell and Gene Therapy Consortium? From your perspective, what are the keys to maintaining these productive long-term collaborations?*

**Stephanie Cherqui:**
I am not an MD myself, but when you go from bench to bedside, you have to be surrounded by a strong team. It takes a village. It is for this reason that I created the Cystinosis Stem Cell and Gene Therapy Consortium. I chose really amazing people who were willing to give their time, because they give a lot of it, to advise and support us at every step of the way. They helped us navigate the regulatory processes to develop a new clinical trial, which can be complicated when it involves stem cells and gene therapy. It was the first of its kind at the University of California San Diego. It was also important to involve the patient advocacy group. Nancy Stack, the president of the Cystinosis Research Foundation, is also part of this consortium. They are an essential part of it because you need to have someone who speaks all the "languages". They are the best people to help us navigate the disease landscape and guide us on the appropriate end points, and really explain what the families are truly struggling with. I am lucky with this consortium as we keep the dialogue open. We held meetings and brainstorming sessions to determine the best clinical trial design and most meaningful end points. Now that it is completed, I can say it was a challenge, but it always moved forward thanks to a group of expert and kind people. Consortia like this are really key for these kinds of clinical translational projects.

**Erica Berg (*host*):**
*Kerry Jo, I wanted to talk a little about FDA's Rare Disease Innovation Hub. How does that help facilitate these types of cross-disease collaborations and what sort of outcomes are you hoping for with the program?*

***"The Hub, in terms of outcomes, is hoping to foster a number of public workshops called the Rare Disease Innovation Science and Exploration Public Workshop Series, also known as the RISE Public Workshop Series. These workshops are really intended to address challenges that are common to multiple diseases or across classes of diseases to think about how we can apply evolving science into innovative solutions that will accelerate rare disease therapies."***

**Kerry Jo Lee:**
The Rare Disease Innovation Hub is really an important advancement in how the FDA looks at cross-sectional issues in rare diseases. I will start with a little bit of history, as it may be confusing to people, and then talk about how the Hub builds and enhances upon what we have. Since about 2013, the centers have had staff dedicated to working across rare diseases: the Rare Diseases Team in CDER and the Rare Disease Program Staff in the Center for Biologics Evaluation and Research (CBER). We have collaborated and still do on many programs, such as the Rare Disease Endpoint Advancement Pilot Program, to develop endpoints, the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Program, which is very important, and even within CDER, there is the Accelerating Rare Disease Cures (ARC) Program, which is led by cross-disciplinary leadership across our clinical pharmacology and statistical offices. The enhancements through the Hub really reflect a much-needed focal point for the broader rare disease community where they can engage, access, and provide input and have bi-directional engagement with the FDA on matters that span the centers that are of importance to rare disease drug development at large.

The Hub, in terms of outcomes, is hoping to foster a number of public workshops called the Rare Disease Innovation Science and Exploration Public Workshop Series, also known as the RISE Public Workshop Series. These workshops are really intended to address challenges that are common to multiple diseases

or across classes of diseases to think about how we can apply evolving science into innovative solutions that will accelerate rare disease therapies. As part of that bi-directional engagement that is so critical for the Hub, the public will be able to submit topics for consideration for these workshops. So we are listening. The Hub is really here to help facilitate dialogue and move the field forward, beyond just one center.

**Erica Berg (*host*):**

*So, switching gears again, we are going to talk about the underlying structures that make all these types of collaborations possible. Daria, could you share how we can better leverage data sharing platforms, registries, biobanks, and all of these resources to support research across rare disease boundaries?*

> ***"The goal is that every resource that is being added onto this platform becomes interoperable and what we call FAIR, which means findable, accessible, interoperable, and reusable. This is the only way to make the different resources visible and reusable, because if they are siloed or constructed in a way that does not follow the FAIR principles, we lose a lot of valuable data."***

**Daria Julkowska:**

In my opinion, in order to truly leverage those different types of data, there are three main elements to consider: interoperability, common standards, and ontology. The idea is, and this is something that we also implemented through the development of the Virtual Platform of Data Tools and Resources, that there is a place where you can easily find the different types of data. For example, there are catalogs that contain information on rare diseases, but there is also genetic data, biobanks and registries that are being connected. The goal is that every resource that is being added onto this platform becomes interoperable and what we call FAIR, which means findable, accessible, interoperable, and reusable. This is the only way to make the different resources visible and reusable, because if they are siloed or constructed in a way that does not follow the FAIR principles, we lose a lot of valuable data. We have also extended and created what we call the WikiPathways, and this is where interdisciplinarity is essential as you need biologists, chemists, but also clinicians and bioinformaticians, working together to create the rare disease pathways. These pathways can help accelerate the identification of the drug targets and improve the understanding of the disease mechanisms, but can also support efforts like drug repositioning. It really requires interdisciplinary collaboration, but also, and this is very important, the standardization and interoperability of different types of data.

**Erica Berg (*host*):**

*Does anyone else have any experience with these types of registries that they would like to share?*

**Kerry Jo Lee:**

FDA supports the Rare Disease Cures Accelerator Data Analytics Platform, which is a repository where all types of data can be submitted and curated for querying, to understand many of the things that were just discussed. I cannot underscore enough the point that was made about interoperability. As Julian mentioned, capturing the rare disease patient experience is critical. You could be missing a couple of data points and have an entirely different picture of what you need in order to bring a therapy successfully to market. The other thing that I would underscore is when you are building these databases, you must first think about what question you are trying to answer, and ensure that those elements are built in, and that you are collecting those elements into your program. From a regulatory context, are you collecting the endpoints that are relevant? Are you collecting correlation between biomarkers and clinical outcomes? Are you capturing clinical characteristics of these heterogeneous populations that will be important to defining the patient populations? All of those elements become really important. You have to start off with a plan in mind and ensure you are building to answer those questions you have previously defined.

> ***"Standardization and collaboration are crucial. As we have been saying, the challenge is how to get enough data, how to understand that data, and then how to extrapolate information from it. There is still a long way to go in terms of how we can increase that standardization."***

**Julian Beach:**

I think one of the things that you do have to look at is simplicity as well and how effective it is to use the data. The more data that you collect and want to analyze, the less useful it can become. So it is really about looking at key survival outcomes. When you start looking across national boundaries and pooling that data, you need to consider the ethical and legal standards that go along with this information as well. In the global context of rare disease numbers, you may have N=10 patients for a particular rare disease in each country and pooling the data gives you a total global population. However you need to be looking at things from a different perspective than we have in the past. Standardization and collaboration are crucial. As we have been saying, the challenge is how to get enough data, how to understand that data, and then how to extrapolate information from it. There is still a long way to go in terms of how we can increase that standardization. Even when you look at an ecosystem like the UK, where you have a common health standard, a unified health system, and the Clinical Practice Research Datalink (CPRD) service, which brings together all of the information within the UK, there are still things which can be added. Registries and other tools continue to be layered on top. So the question is: how can we ensure that simplicity is built into the system as well?

**Erica Berg (*host*):**
*Julian, from a regulatory standpoint, is there ways that agencies can better support or even incentivize the development of therapies and treatments that have cross-disease potential?*

**Julian Beach:**
I think if I start with the original approach, there are definitely ways that people can see how ecosystems can align. Within the UK, we have something called the Innovative Licensing and Access Pathway (ILAP). That brings together key elements like regulatory approval, funding approval, and then the actual use of the medicine. It essentially streamlines access so that patients can receive these products much more quickly. It is about aligning those processes. Then, if you are looking at how to build on the original filing, to repurpose that medicine for a different use, for example, there are opportunities to draw on prior knowledge. This could include clinical or quality data, how you make the medicine, endpoints, or non-clinical effects. The key is determining the translatability. From a regulatory standpoint, we can be clearer when using generic wording such as "pathway designations", because I do not believe that they provide a panacea without having some definition around what that platform actually entails.

**Erica Berg (*host*):**
*Stephanie, I was wondering if you could share from your perspective what you think are the key barriers that prevent more widespread cross-disease collaboration and have you seen any creative solutions that have worked to bridge those silos?*

***"People who are creating or organizing these biobanks are sometimes not very willing to share. Sometimes it can be complicated as there is a sort of competitiveness. We all want to collaborate and share, but you also want to be the first. So that exists and we have to be honest about it, as it could be a barrier in cross-collaboration in the rare disease field."***

**Stephanie Cherqui:**
One example is biobanks or repositories of tissues and blood. These are crucial in rare disease research, but they are costly. There are some national biobanks that are supported by federal funding, but as we said, rare diseases involve very few patients here and there, and we cannot have tissues or blood for all the disorders. Most of the time, they are created by a specific research group at a specific location and are supposed to be available to the public, but this is not always the case. For Friedreich ataxia, for example, it has been more than a year that I have been trying to acquire some tissue that is supposedly available, but going through the MTA (Material Transfer Agreement) process and accessing it is very complicated. People who are creating or organizing these biobanks are sometimes not very willing to share. Sometimes it can be complicated as there is a sort of competitiveness. We all want to collaborate and share, but you also want to be the first. So that exists and we have to be honest about it, as it could be a barrier in cross-collaboration in the rare disease field. I think the key people in that landscape are the advocacy groups, because they have the opportunity to bring together the researchers, scientists, and physicians working on a specific disease through symposium or workshop events, and then we are all together in a room and we have to discuss and share our data. Usually, that is a key component needed for collaboration. I think there is definitely much more to be done in that field.

**Erica Berg (*host*):**
*Kerry Jo, I wanted to talk a little about regulatory pathways. Given the Hub's cross-center role, how do you approach aligning priorities and regulatory pathways between CDER and CBER, to support the cross-disease initiatives?*

**Kerry Jo Lee:**
I think the Hub is a fantastic addition in terms of enhancing and strengthening our communication. It provides a visible and tangible connection point, not only for the external community, but for us within the agency as well, for dialogue, information sharing, and harmonization between the two centers. I would say that our priorities are already aligned. We want to speed up and increase the availability of safe and effective therapies for the rare disease patient population. What the Hub does is provide those vital connections and structures, internally. For example, there is the Rare Disease Policy and Portfolio Council now under the Hub, which I co-chair with another colleague from CBER. That is a designated forum where we can connect, collaborate, and discuss our portfolios and how we can evolve our shared initiatives in lockstep towards our common goal.

**Erica Berg (*host*):**
*I wanted to spend a little time now talking about funding issues. Daria, given your experience with European funding schemes, what structural changes do you think would best incentivize or reward interdisciplinary research in rare disease?*

**Daria Julkowska:**
Honestly, for the interdisciplinary research, we already have a lot of different types of collaboration. For example, in our case, having complementary disciplines or partners is something that is mandatory when you are applying for every funding opportunity. There is perhaps one field which I believe is really lagging behind, and that is the field of social sciences and humanities, including socioeconomic aspects. This is where the rare disease community, particularly on the medical side, is not yet used to collaborating with sociologists, economists, and so on. I believe that this is where we need to make a stronger effort when talking about interdisciplinarity.

***"If we want to accelerate the development of treatments for rare diseases, knowing that 95% of them still lack an effective treatment, we must acknowledge that we will not be able to develop one treatment per disease. I think it is important to focus efforts on building more knowledge and gathering communities together. This can be done through the specific funding opportunities and also by stimulating innovation through public-private partnerships."***

Another important aspect is to talk about cross-disease research, because in my opinion, this is not yet something that is fully anchored in our way of thinking. We still think about rare diseases by focusing on individual diseases or groups of rare diseases. We need to come from a different perspective, so that we are reducing the number of rare disease categories and finding the commonalities. This is something which is not yet sufficiently put forward. If we want to accelerate the development of treatments for rare diseases, knowing that 95% of them still lack an effective treatment, we must acknowledge that we will not be able to develop one treatment per disease. I think it is important to focus efforts on building more knowledge and gathering communities together. This can be done through the specific funding opportunities and also by stimulating innovation through public-private partnerships. The collaboration with industry, in this area, is extremely important. We must not forget the third side of the triangle where we include the regulatory agencies or health technology assessment bodies from the very start when thinking about this type of research. I am sure that Kerry Jo and Julian would agree on this point. Because if we continue thinking in terms of one treatment equals one condition, then we will face serious bottlenecks when trying to implement cross-disease approaches. So, I think what is really important is sharing knowledge, driving systemic change in how we think about rare diseases, and then supporting innovation and funding in this respect.

**Kerry Jo Lee:**
I wholeheartedly agree about thinking about the regulatory component early on.

**Julian Beach:**
Agreed. I think Daria's comment about the HTA involvement occurring early on and approaching it collaboratively is key. It has to be seen as a whole, and I think this is very much an evolving space for rare therapies in terms of how we can then distribute them into the health systems.

**Erica Berg (*host*):**
*We were saying that there needs to be a systemic change in how people view these cross-disease approaches more generally. Any thoughts on how that could be achieved? Is it a regulatory issue, a policy change, a shift in how researchers think, or a little bit of everything?*

**Julian Beach:**
I think it is a bit of everything. I think it involves really looking at the risk paradigm that needs to be considered to make informed decisions involving patients. At what point can a medicine be used? At what point is a product safe? Equally important is having that does-it-work comparison, and for how long? Those are the types of things that you can do in the short term, but having some really clear systems for post-market surveillance and follow-up is also important. Once you have had that treatment, when does it come back into that pharmacovigilance space? All of these factors are really critical to enabling earlier access to treatments and therapies.

**Kerry Jo Lee:**
I think a part of your question was asking how we take these experiences and translate them more broadly to the community. We think about that a lot and it takes all of us buying into that. I think the rare disease community, external to regulators, needs to come together as a broader community and understand that the individual condition and the therapies designed to help are unique, but the challenges that you are going to face are common. "How do I adapt a clinical outcome assessment for my disease?" "What is the level and degree of translational science that I need to support my biomarker?" "What types of innovative statistical designs can I employ?" "How do I incorporate real-world data to augment my applications?" Those are issues that go beyond the individual diseases. I think the more we do to share those approaches, the more helpful those approaches will hopefully be to others.

**Erica Berg (*host*):**
*Looking ahead 5 to 10 years, what does a mature, thriving, and cross-disease research ecosystem for rare disease look like? How do we get from here to there? Stephanie, let us start with you.*

***"When you prove the safety of a technology for one rare disease, the goal would be to streamline the process so that it could then be applied to more diseases, with only minimal safety studies needed to bridge the gap from one disease to another. If this kind of platform was widely accessible to many, I think it would really accelerate the process and change the landscape of how we use gene therapy for many disorders."***

**Stephanie Cherqui:**
So in regards to gene therapy, the main challenge is the manufacturing and the technology needed to optimize safety. They are the most costly and long studies to carry out. One of the best ways to really use the resources in a way that we can apply to many disorders is through the platforms. I know that the FDA is really supporting that now. We want to be able to apply a technology to many of our disorders. When you prove the safety of a technology for one rare disease, the goal would be to streamline the process

so that it could then be applied to more diseases, with only minimal safety studies needed to bridge the gap from one disease to another. If this kind of platform was widely accessible to many, I think it would really accelerate the process and change the landscape of how we use gene therapy for many disorders. I am sure this is true not only for gene therapy, but I think the platform and streamlining the regulatory process would be the key.

*"I would say that the ideal kind of ecosystem is, first of all, focused on the needs of patients. They are really the drivers of this ecosystem and it encompasses all the elements of the pipeline: from the fundamental research until the end of the process. And when I say the end of the process, it is not when the drug or therapy is approved, but when it is actually accessible to patients."*

**Daria Julkowska:**
A few weeks ago when I was in a meeting, somebody said that rare disease patients do not see the timeline in the same way. So for them, especially when it comes to the diagnosis, even a short delay, like a weekend, is too long. It is too long because it hampers the time to receive the diagnosis. I would say that the ideal kind of ecosystem is, first of all, focused on the needs of patients. They are really the drivers of this ecosystem and it encompasses all the elements of the pipeline: from the fundamental research until the end of the process. And when I say the end of the process, it is not when the drug or therapy is approved, but when it is actually accessible to patients. So for me, in this ideal ecosystem, there is also more of a focus on innovation that allows for the acceleration of this access. And for that to occur, we really need to collaborate with all stakeholders. I believe that we are on the right path, especially when it comes to this inclusion of the regulators, the industry, and the HTA. There is currently more and more dialogue about this, so I believe that in five to 10 years, we will get there.

**Julian Beach:**
It is a really exciting question because I think innovation is growing at such a pace that when we think about the 5- or 10-year outlook we have got to ask: how do we ensure that the right structures and funding are in place to enable regulators, innovators, and industry to reduce the time from discovery to patient? And how can we make sure that prior knowledge and information sharing across different disease types is clearer and less ambiguous? From a UK and European standpoint, there are a large number of regulations that were written 25 or more years ago. We need to think about how we can update them to make them have a more patient-centric approach, as Daria has clearly articulated. For me, the key is looking at how do we maintain patient safety, while making sure that the risk assessment is proportionate, and most importantly that patients are involved in the definition of risks. I think those are the biggest changes I see, which will enable innovation to move forward.

Obviously, there are the technological things and the other parts that will enable it, like AI, machine learning, and data sets, as we have been discussing. But those kinds of advances are built on a strong regulatory foundation, the involvement of all stakeholders and a supportive ecosystem.

*"Rare disease drug development is complex. There are challenges that always arise and in this space, there are a lot of firsts. I really think that we can use the experience of others to help navigate the community. That way, when you hit those roadblocks and those complexities you are able to navigate them more nimbly and effectively, because the end goal is ensuring we can get safe and effective therapies to patients as quickly as possible."*

**Kerry Jo Lee:**
I would love to see increased cross-sectional and robust collaboration in the pre-competitive space. To build that prior knowledge before we get into development. I would also love to see a stronger partnership and increased collaboration within the rare disease community, which includes patients, academics, clinicians, sponsors, and regulators, both within individual conditions as well as across different conditions. Rare disease drug development is complex. There are challenges that always arise and in this space, there are a lot of firsts. I really think that we can use the experience of others to help navigate the community. That way, when you hit those roadblocks and those complexities you are able to navigate them more nimbly and effectively, because the end goal is ensuring we can get safe and effective therapies to patients as quickly as possible.

## Building strength together: How rare disease caregivers form communities to support each other and their loved ones

Caregivers of individuals with rare diseases often face unique challenges that can feel isolating, both in terms of the medical complexities they manage and the emotional burden they carry. However, many caregivers are finding strength in community, both within their own disease type and across different disease types, as they share experiences, offer support, and advocate for their loved ones. This panel will explore the diverse strategies caregivers use to form and maintain communities—both in-person and online—and how these communities can provide critical emotional, informational, and practical support. We'll discuss the similarities and differences between in-person and virtual networks, highlighting the unique benefits and challenges each offers. Additionally, the panel will address the important role mental health plays in the caregiver experience, examining how caregiving can affect mental well-being and how community involvement can provide the necessary support to prevent burnout and foster resilience.

Participants will:

- Learn how caregivers of individuals with rare diseases build and maintain supportive communities, both within and across disease types.
- Explore the unique benefits and challenges of in-person versus virtual caregiver networks in providing emotional, informational, and practical support.
- Understand how caregiving impacts mental health and how community involvement can help prevent burnout and foster long-term resilience.

## Panelists

**Marissa Bisho, M.A.**
**CDKL5 in Color, Connecticut, USA**

**Elle Cole, B.A.**
**The CleverlyChanging Podcast, Maryland, USA**

**Jan Domaradzki, Ph.D.**
**Karol Marcinkowski University of Medical Sciences, Poznan, Poland**

**Jennifer Siedman, M.Ed.**
**Courageous Parents Network, Massachusetts, USA**

**Erika Gebel Berg, Ph.D.**
**Science/AAAS, Washington, DC; moderator**

## The Conversation

**Erika Berg (host):**
*Today we will explore the diverse strategies caregivers use to form and maintain communities, both in person and online, and how these communities provide critical, emotional, informational, and practical support. We will discuss the similarities and differences between in-person and virtual networks, highlighting the unique benefits and challenges each offers. Additionally, the panel will address important mental health issues in the caregiver experience, examining how caregiving can affect mental well-being and how community involvement can provide the necessary support to prevent burnout and foster resilience. I would now like to take the opportunity to welcome a truly distinguished panel. I will give each of them a chance to say hello and introduce themselves.*

**Elle Cole:**
My name is Elle Cole. I am a caregiver and a mother to twins. My daughters are 16 years old. One of my daughters has a rare disease called sickle cell disease. Sickle cell disease is one of the most common genetic disorders. However, in the United States, fewer than 200,000 people have this disease, which is why it is considered rare. I am also the host of a podcast, and I am the marketing manager at a sickle cell organization. Thank you for having me.

**Marissa Bishop:**
My name is Marissa Bishop. My background is in social work. I was an elementary school social worker for many years before I had my son. My son Gregory lives with a rare disease called CDKL5 deficiency disorder. It is a developmental and epileptic encephalopathy, which means that he lives with multiple profound disabilities, medical complexities, and a very significant epilepsy disorder. I spent four years volunteering, leading fundraising and community engagement for a CDKL5 foundation, and now I produce and co-host a podcast for our community called *CDKL5 in Color*, where we explore the different symptoms of the disorder, and we welcome our peer caregivers to come on and share their lived experiences.

**Jennifer Siedman:**
My name is Jennifer Seidman. I am a mom to three. My middle son, Benjamin, was diagnosed in 1996 with a lysosomal storage disorder called Sanfilippo syndrome. It is a neurodegenerative disease. If you had met him when he was two, he would have seemed like a typical two-year-old, but by the time he passed away at the age of 17, he was no longer able to walk, talk, or swallow. My caregiver experience changed over time and became more intense. A year after Benjamin passed, I got involved with an organization called Courageous Parents Network, where

I now serve as Director of Community Development. Courageous Parents Network is a nonprofit organization that provides digital resources and programming to help caregivers, and others caring for children with serious medical conditions, to navigate the illness journey with support and a sense of community. At the center of Courageous Parents Network is a video library of over 700 videos featuring the voices of parents and clinicians to illuminate that shared experience and to also help to reduce the isolation that many caregivers experience.

**Jan Domaradzki:**
My name is Jan Domaradzki. I am an assistant professor and medical sociologist at Poznań University of Medical Sciences in Poznań, Poland. I have been researching the social dimension of rare diseases for almost 15 years, with a particular focus on family caregivers. Over time, my research became more personal as for the past 12 years I have been a caregiver for my son who lives with an intellectual disability and autism. Thus, although our experience is fairly different than that of caregivers of individuals with rare diseases, many challenges and needs overlap. In my scientific work I try to advocate for caregivers' needs with my evidence-based engagement.

**Erika Berg (host):**
*I am going to put my first question to Elle. Can you share with us some of the unique day-to-day challenges that rare disease caregivers face?*

> ***"When you have a child that has a rare disease, life is unpredictable. You never know when things are going to change."***

**Elle Cole:**
One of the day-to-day challenges is living in fear of what can happen next. When you have a child that has a rare disease, life is unpredictable. You never know when things are going to change. It means being observant and watching your child. It is also being present in the moment, as you do not want the child's rare disease to consume every moment. You want to be patient. You want to be a loving parent, but you also want to be on top of the medical complexities that they encounter. It is a challenge, to be all of those things. Sometimes you have to be a mathematician or a medical professional. You wear so many different hats. That can be unexpected, as many of us did not go to medical school. Suddenly, we are playing catch-up, doing research, and becoming experts for our children.

**Marissa Bishop:**
I feel exactly the same way. I think that unpredictability is really unique to the rare disease caregiver experience. You have to learn to accept that as your reality. You could have all these beautiful plans for your day or night, and imagine how you think it will go, but the reality is that you are not in control of how it is going to go. Medical things can change on a dime. My son has seizures every day and they can occur at any time. Depending on their severity, they impact what is happening for our family. So, I think that unpredictability and learning how to navigate it in your life is really unique to a rare disease caregiver experience. It is really difficult. It is part of the reason why I am no longer able to work. I have to be available for my son no matter what.

**Jennifer Siedman:**
We hear this all the time at Courageous Parents Network from the families that come to us. They live in what I like to call a chronic crisis existence, where you do not know what is going to happen next. Maintaining that level of hypervigilance is exhausting. I think we forget to think about the exhaustion factor that comes from so much of what we have to do. The world is better at recognizing the physical or visually apparent factors, but less adept at recognizing the mental exhaustion that comes on when we live through these experiences.

**Erika Berg (host):**
*Jan, over the past decade, you have done a lot of research into the needs of caregivers for people living with rare diseases. Based on what you just heard, could you share some of your findings in terms of what issues caregivers face and what broader impact that can have on their well-being and mental health?*

> ***"Our research confirmed that although rare diseases differ significantly in their epidemiology, etiology, symptoms, and prognosis, most stressors or challenges faced by caregivers are quite similar and include physical strain, emotional exhaustion, and feelings of loneliness."***

**Jan Domaradzki:**
In recent years, I have conducted several research projects on specific rare including Dravet syndrome, Angelman syndrome, 22q11 deletion syndrome, and Duchenne muscular dystrophy. We have also conducted two large nationwide surveys, each of which included over 950 caregivers providing care for over 1000 children with rare, ultra-rare, and even hyper-rare diseases. Our research confirmed that although rare diseases differ significantly in their epidemiology, etiology, symptoms, and prognosis, most stressors or challenges faced by caregivers are quite similar and include physical strain, emotional exhaustion, and feelings of loneliness. What is important is that family dynamics, both in terms of the relationship with a partner or spouse, and with the healthy children, are seriously affected. Caregivers frequently do not have time for themselves. There is a serious gender gap. We find it here in Poland, but it is also typical for many other countries. For many reasons, including cultural ones, it is frequently women who devote themselves to caregiving, which can be 24/7. They often have to quit their job entirely, which is of course

also quite challenging for them. One of the most important challenges is their experience or contact with the healthcare system, which is frequently very overwhelming. Many caregivers feel that they are invisible to the system because in many countries, including Poland, healthcare professionals frequently focus on the disease or on the patient themselves, while the caregivers' needs are overlooked. To give you a couple of numbers, for example, our research shows that up to 90% of caregivers experience chronic stress, 77% experience depression, and 66% experience anticipatory grief, which Jennifer also mentioned and is a form of chronic stress. Many feel lonely and misunderstood by those around them, even by their closest family and friends. So, what is important to remember is that caregiving for a person with a rare disease creates a multidimensional burden that affects the physical, mental, psychological, emotional, and social health of caregivers.

**Erika Berg (host):**

*Marissa, you recently wrote an article for Rare Revolution Magazine describing your experiences in trying to find community as a parent and caregiver for a child with a rare disorder. Can you talk about those early days and some of the challenges you faced in getting the support or connection you needed from families that were not grappling with those issues?*

> ***"I found it really difficult to connect to the moms who were having a more traditional parenting experience. So, it was very isolating, not only socially, feeling like I was not able to connect with them, but even physically."***

**Marissa Bishop:**

When my son was born, I did not know that he had a rare disease. In the grand scheme of things, we were lucky. We got a relatively early diagnosis. He was diagnosed at six months old and I know that many people have to wait many more years. Initially, I did not know what was going on with him. He started having seizures at four weeks old, but like a lot of new moms, I had wanted to make new mom friends and had joined some of the Mom and Me groups in my local community. It became evident really quickly that it was going to be harder to build those relationships than I had anticipated. I would go to the groups and as the other moms wanted to talk about milestones or sleep training or things like that, I was wondering if I needed to switch neurologists for my baby and if I should be starting feeding therapy and early intervention. I found it really difficult to connect to the moms who were having a more traditional parenting experience. It was very isolating, not only socially, feeling like I was not able to connect with them, but even physically. I would be in the same space as these women and as their babies started to grow, develop, crawl, roll, run and move, the moms were busy with their babies. At the same time I was still sitting in my same place, cradling my toddler and giving him a bottle because he was not able to eat food orally. As time went on, the disconnect between our experiences grew wider, and I found myself no longer willing to try to fit in. That is when I had to pivot and find other mothers who were living a similar experience as I was.

**Erika Berg (host):**

*Jennifer, when you first assumed the role of caregiver in the rare disease community, how did you figure out where to turn for advice, support, and guidance?*

**Jennifer Siedman:**

When Benjamin was diagnosed in 1996, the internet was fledgling. There were no social media groups that you could join and finding families that were on a similar path was very difficult. Like Marissa, I also felt separated from the typical mom. I could not stand in the pickup line at elementary school and talk about my experiences with Benjamin with the other parents, because they were so disconnected from the typical parenting experience. You had to make an effort to lean in and go to patient organization conferences. Those could be scary too because sometimes while you may feel embraced by being around others that know and see you, you also see into your future or what might be coming. That can also be emotionally challenging. One of the things I love about Courageous Parents Network is that you can go on the website and watch a video of another parent talking about their experience. If it is not resonating with you, you can simply turn it off and pick a different story to listen to, unlike at a live conference. Live conferences can be great, but sometimes you have to be in that same space with everyone. So, I like to think of Courageous Parents Network as a place where you can "try on" the caregiver hat that works best for you by listening to different stories and hearing about the similar experiences and emotions that you are encountering along your path. Unfortunately, Courageous Parents Network did not exist when I was caring for my son, Benjamin. It was only a year old when I got involved. So, I have helped build the organization that I see is now impacting not only families of children and caregivers, but also the clinicians who support us along this journey by caring for our children and hopefully caring for us as caregivers as well.

> ***"For my very first Mother's Day, my husband brought me a computer and said, "I think you should blog." I did not really know much about it, but I love to write. So, I said, "Okay, the community does not exist, so I am going to create it." I started writing my story and sharing my experiences. I then started to find other parents who would sometimes comment, and they would connect with me. Even though our stories were somewhat different, there was a commonality there."***

**Elle Cole:**

What you said really resonated with me because when my daughter was diagnosed, it was a unique experience, as there was no one else in my family who had sickle cell disease. I could not

explain it well enough and even though I tried, they did not necessarily understand. I was not an online media person and I did not have social media at the time, but that was really the door I opened to start embracing the idea of finding a community. I actually started with my blog, cleverlychanging.com. For my very first Mother's Day, my husband brought me a computer and said, "I think you should blog." I did not really know much about it, but I love to write. I said, "Okay, the community does not exist, so I am going to create it." I started writing my story and sharing my experiences. I then started to find other parents who would sometimes comment and they would connect with me. Even though our stories were somewhat different, there was a commonality there. I was willing to be open in order to get to know other people. My daughter was diagnosed at newborn screening, so I knew almost immediately as they confirm it at the three-month mark. I received a letter in the mail and the letter stated, "Your child has hemoglobin SS." It was such a cold and isolating experience. Even though I have a husband who is very supportive, I felt like I was experiencing everything alone. I knew that if I stayed in that state of mind, I would not be productive. I remember the day I got the letter, I looked down at my twin girls as I was feeding them and I remember seeing my daughter smile. That was really the light bulb moment that said, "You can do this. You can figure this out. You can try." And what trying looks like is different for everyone, but that is when I had the courage to not give up and to get out of the house. I started to open up and be honest with myself that this was a real diagnosis. Sometimes I think at the beginning, you are in denial. Specifically with the rare disease my daughter has. Until she experienced her first pain crisis, I think I was in denial for some time. During her first crisis, when the blood starts to sickle and it becomes hard and sticky, she was in a lot of pain. It was not something that I could change. I could not control it. I could not remove it. I gave her the medication like the doctor said, but it was still there. That was when it became real for me and I found other parents by talking to the doctor. They said these support groups exist, but I never could find those particular support groups. I went online and found people who were like-minded and, like Jennifer said, I started to go to conferences. My first conference was in 2019, when my daughter was 11. It was an eye-opening experience, and I felt like these were my people. I felt like it was a family reunion and I felt accepted. That was when I decided that advocacy was something that I would continue and become a part of, and I would usher in new parents. I would get to know them so they did not have the same isolating experience as I had. That was really a groundbreaking moment in my family's life.

**Erika Berg (host):**

*Jan, from a research perspective, have you looked at what the newly diagnosed entering the rare caregiver community are typically doing in that space when they are trying to reach out? Or is that an unknown?*

> ***"Although in some cases, physicians serve as types of guides who point to a particular patient association or foundation, in most cases, families found themselves navigating their reality totally alone."***

**Jan Domaradzki:**

What was just said is also reflected in our research, as well as in global studies. Due to the rarity of these conditions, most caregivers describe the initial post-diagnosis phase, like Marissa did, as marked by confusion, fear, loneliness, and lack of direction. Although in some cases, physicians serve as types of guides who point to a particular patient association or foundation, in most cases, families found themselves navigating their reality totally alone. For example, nine of the 11 associations I am collaborating with said that they had to create their own association because there was nothing that existed. The key turning point frequently comes through online networks, such as online support groups or social media pages, or sometimes through a chance encounter with another parent, for example on the hospital ward. This often leads to creating or joining patient advocacy groups because caregivers frequently describe their experience as a lonely ride, where they are left by themselves and must unite without the official support from the state or other agencies.

**Erika Berg (host):**

*Marissa, in that same article I mentioned before you talked about how you had mixed feelings around traditional social media networks like Facebook. Can you share how you feel about those social media networks, including the pros and cons, and let us know where you ended up finding your community?*

> ***"I feel like Facebook is the go-to place for community support for rare diseases, especially the extremely rare diseases. It is free, it is accessible to almost anyone, and if you have good moderators, it can really be a positive experience to be a part of those groups."***

**Marissa Bishop:**

When my son received his diagnosis, the genetic testing was ordered by his neurologist. When it came in, the neurologist called me on the telephone. I remember he said, "We know why your son is having seizures. He has a mutation on the CDKL5 gene." And I am trying to write it down: CDKL5. I had never heard of anything like that before and he said, "We can talk about it more, but I do not know a lot about it." That was the end of the phone call. The first thing I did is I went on Google and I typed in CDKL5, and there was a foundation that already existed. I do not know if my neurologist had checked Google before he called me but I wish he would have told me, "There is a place you can go to find other people." So, I found our foundation through Google.

The next thing I found was the Facebook support group. Our Facebook support group has been in existence for over 10 years and there are pros and cons to social media. I feel like Facebook is the go-to place for community support for rare diseases, especially the extremely rare diseases. It is free, it is accessible to almost anyone, and if you have good moderators, it can really be a positive experience to be a part of those groups. You are

sharing photos and stories, you are asking questions, and you are receiving immediate feedback. I can post a question in our Facebook support group and hear back in an hour from multiple people, as opposed to trying to ask my doctor and wait days to hear back from him. Of course, I would not take medical advice from the people in the Facebook group, but if you have something on your mind, you can get feedback pretty quickly. I think other social media, like Instagram and TikTok, are fabulous for following content creators who reflect your lived experience. When I step outside of my house, I do not see other families that look like my family, but I follow a bunch of content creators on Instagram who are sharing videos of their kids and their day-to-day lives. When you can see somebody else having a similar experience, it really goes a long way in helping caregivers feel less alone. One of my favorite things about social media is the tips, tricks and hacks that you learn from other parents. This is the stuff that healthcare providers are not able to share with you. They just do not know the accessibility hacks, equipment hacks, or gift ideas, because buying gifts for kids with severe neurodevelopmental disorders is really hard. Being able to share, "I found this and my son seems interested," is really helpful. The biggest con for me is the fact that, especially with the Facebook support groups, those groups do not belong to the community. They belong to Facebook. Facebook can cancel them and delete them at any time, which would be devastating to communities, not only for the loss of the connections that you have made with other people, whom in reality you do not have another way to contact, but for the information that exists in those groups. For example, when my son's neurologist recommends a new anti-seizure medicine for him, one of the first things I do is type the name of the medicine in the Facebook search function in our group. I read all the questions and comments and experiences that people have shared about that medication. I am then able to take that back to the neurologist and say, "People are saying this about the medication. What do you think about that? Have you heard that? Have you experienced that?" There is over a decade's worth of that type of information in that group and it is an extremely valuable resource for families that does not exist anywhere else. However, it does not belong to the community and the families, and it is at the mercy of Meta.

***"In my community, there are so many different nuances that needed to be changed or updated and social media helped us to become more unified."***

**Elle Cole:**

I think social media really helped me develop a larger community where I started to meet people in my own state. Prior to social media, I just felt like everybody was so far apart. Once I started to attend those conferences, I started to meet people that were in my area and I started to be able to connect with them at home. Even though I do not necessarily see them, I am able to text them, like in a more intimate setting. I wanted to be able to learn how to share my story and to engage in legislative advocacy, and social media put me in touch with people who were already doing it. It made me feel that I could be a part of a larger system change. In my community, there are so many different nuances that needed to be changed or updated and social media helped us to become more unified. I also now work for a nonprofit in California that is related to sickle cell disease, and I would not have that job without social media because that is how they found me. We were on a board together and we were able to connect with each other. It not only widened my voice, but it helped me see that even though my area was not doing as many things as some of the others of the organization, we could create those things locally. So, it gave me a vision of things to work towards and things that I could work with other people to create in my local community. It really just expanded our horizon and connected us all with each other. June 19th is World Sickle Cell Day and we have a 24-hour global marathon that I now get to help plan. I meet people from all over the world who have this rare disease and it has given me so much hope and courage about the future that I did not have before. For me, it has been one of those experiences where you start out with dreams and goals, but when you first get that diagnosis, it feels like they slip away. Then, when you have a community, all of a sudden it feels like you are being given that gift back. You are able to regain those dreams, regain those goals, or develop new ones that are in line with your future. So, I know that it is quite complex, but it has really been that way for me and my family.

**Erika Berg (host):**

*Jennifer, I want to talk more about the Courageous Parents Network as before you joined, you were involved with the network as a parent. Can you talk about how you benefited from connecting with Courageous Parents Network during a difficult time and what inspired you to eventually do the same for other families and continue on with this work as Director of Community Engagement? What is special about this organization?*

**Jennifer Siedman:**

First, I want to touch on something that both Marissa and Elle mentioned, which is the gift that the internet has given us and acknowledge that sometimes that gift can be a burden. One of the things that I also want to highlight, which is exceptional about Courageous Parents Network, is that clinicians come to us to understand the lived experience. I think the capacity of the internet now, through places like Facebook, TikTok and Instagram, allows us to show the world how we are living robustly and happily. Although there are a lot of challenges, we are actually living a life that is whole and good. I think it is important and it has provided an opportunity for those in the medical field to learn about our lived experience without having to be in front of that patient 24/7. So, you can now get your doctor to understand what your child looks like at home because you have the capacity to send a video.

As I said, when I first came to Courageous Parents Network, it was only a year old, and I did benefit from speaking about my experience of caring for my son Benjamin. My interview is with my husband and our palliative care doctor. We talked a lot about how palliative care changed the care experience of my son. He did not get a referral until he was 14 years old, and we were in a medical crisis at the time, which is another discussion, because I believe we should have been referred much earlier. I think our lives and our journey would have been much better if we had received palliative care sooner. It is one of the things we advocate for at

Courageous Parents Network. I gained a whole new community after I started getting involved with Courageous Parents Network because, obviously, I have the opportunity to meet so many parents with so many different diseases. I get to see and study the similarities that we all share and have in common, because even though it is nice to spend time in your own disease group and with people whose diagnosis is similar, we all have so many shared experiences across the board. We have all experienced anticipatory grief. We all worry about maintaining our partnerships, whatever that looks like. We all think about how to have good doctor-patient interactions. These are all the kinds of topics we talk about on Courageous Parents Network. So, it has been nice for me to extend my relationship with my son Ben and continue my bond with him, so to speak, even after his death, through my work at Courageous Parents Network.

**Erika Berg (host):**

*Jan, do you know to what extent clinicians are accessing these online communities for information that they can bring into their practices? Is it a part of formal training or clinical recommendations, or is it more used on a case-by-case basis, based on what you have seen in your work?*

> ***"Research from many parts of the world shows that numerous healthcare professionals, including nurses, physical therapists, and physicians of various specialties, often lack knowledge and awareness of rare diseases."***

**Jan Domaradzki:**

Research from many parts of the world shows that numerous healthcare professionals, including nurses, physical therapists, and physicians of various specialties, often lack knowledge and awareness of rare diseases. Research also shows that even if they are aware of rare diseases, they frequently feel unprepared to provide care for such individuals and their families. It is for this reason that most associations, foundations, or patient advocacy groups try to educate not only parents, but also healthcare professionals. Most are eager to learn from the parents or the so-called "lay experts," because as we have over 10,000 rare diseases, it is impossible for physicians, whether they are general physicians or specialists, to be familiar with such a large group of diseases. They frequently acknowledge the expertise of parents, although, sometimes they neglect this knowledge. Most associations and foundations try to educate healthcare professionals, and many healthcare professionals try to use this expert knowledge to support their future patients. For example, they send patients or newly diagnosed families to different associations or organizations, and also try to participate in different seminars, webinars, and conferences. Each association or organization tries to have their own researchers who support their knowledge. So, there is a close established link between associations, parents, and the scientific community.

> ***"We spend a significant amount of time presenting at hospital organizations because we understand that if we can change the dynamic within the medical system, we can change the caregiver experience. It is a critical piece, and we are really setting out to transform care, both how it is given and received, by educating both clinicians and parents."***

**Jennifer Siedman:**

I would like to add that at Courageous Parents Network, while we are by parents and for parents as an organization, when we host our monthly webinars on various topics, generally at least 50% of the people who attend are clinicians. They are coming to us to learn about the lived family experience through the programming that we provide and through the videos that we have. We spend a significant amount of time presenting at hospital organizations because we understand that if we can change the dynamic within the medical system, we can change the caregiver experience. It is a critical piece, and we are really setting out to transform care, both how it is given and received, by educating both clinicians and parents.

**Elle Cole:**

I also wanted to add that my daughter was born in 2008, and now I see an explosion of patient-centered organizations and community advocacy boards. You are now seeing a lot of hospitals that are asking patients and caregivers how they feel, and they are able to sit on boards and have direct input about the future and what needs to change. At first it was very different, but I am seeing more openness and willingness to do this. Often, the people who serve on these boards are recruited from other organizations in the community.

**Erika Berg (host):**

*Elle, you have written about the importance of mentorship for rare disease caregivers. Can you talk about making connections with experienced people who can help navigate the practical and emotional challenges of day-to-day life, and share some resources that could help others to establish those types of mentorship-like connections?*

> ***"Conferences are absolutely amazing, and I have met lifelong friends at conferences. I would say that if you are able to attend a conference, it is one of the best places to meet someone you can mentor and be mentored by."***

**Elle Cole:**

Let me start by sharing my story with mentorship. I mentioned that my daughter was diagnosed at birth with her rare disease,

but when she turned six years old, she was also diagnosed with an autoimmune disease, called type 1 diabetes. When we went to the hospital for type 1 diabetes and we were in the emergency room, they gave me a paper and told me to sign up because I would be connected with a parent mentor. What was amazing about that is when she was released and I got home, another parent of a child with type 1 diabetes called me and said, "Right now it seems hard, it seems impossible, but you can get through this. You can learn how to give your child the medication that they need to live and do not give up." That was so unique because, again, this was not my first experience with chronic illness, but it was the first time I was immediately put into direct connection with someone who said, "You can handle this." And I said, "Wow, this is amazing!" I was also given what was called a bag of hope. In that bag of hope there was a teddy bear, books, and different things related to treatment, and I thought that was amazing, but it was not something that I received on the rare disease side. It was at that moment that I thought how wonderful it would be if this existed for everybody, so that you do not feel like you are isolated or alone in this experience. For me, it was an eye-opening moment where I began to write my book. I had already started teaching my kids, but I realized I needed to publish the books and the information I was sharing with them. I needed to create something for my rare disease community like the type 1 diabetes community gave me. So, I started to talk to the organizations and say, "This was my experience in this setting, what can we do to make it better?" We have tried to create what is called the Sickle Cell Caregiver Summit to give parents an opportunity to connect with other people. We do not yet have a system where you can sign up immediately when you are in the hospital, and I would love to get to that point, but we are not there right now. What I do, however, is actively work to create a space where parents can directly mentor each other. And that was because of my unique experience. To be completely honest, because my child had a dual diagnosis, I felt like I could not 100% relate to the rare disease community in the same way. I thought that she is going through all of these other experiences that are so different and unique, but now I realize that it is okay that we have some things that are different. We are all working towards keeping our children as healthy as possible and giving them the best quality of life, and that is what truly matters. When it comes to mentorship, it is something where you may have to reach out to organizations. I know it is hard when you are handling so much and trying to create your own organization, but sometimes that can help serve as the foundation of a mentorship. There are organizations like the Caregiver Network and the one I work for, which is called the Cayenne Wellness Center, where they will connect you with a support group. There, you can talk to caregivers or patients and just have a safe space to be honest and real. Those are the opportunities that do exist in the community. Global Genes is another community where you can connect with other people, and I know Jennifer mentioned conferences as well. Conferences are absolutely amazing and I have met lifelong friends at conferences. I would say that if you are able to attend a conference, it is one of the best places to meet someone you can mentor and be mentored by. It can be a cyclical relationship. It does not have to be one-sided. There are people who are giants in this community who have done it before, and you can lean on each other's shoulders.

**Marissa Bishop:**
I think the idea of having a mentor and having a mentor relationship is such a gift. It is a gift for the person who is experiencing the information and the support because this is new for them. As I have grown, and my son is 9 now, I have leaned on the mentors and the people in the CDKL5 community who have come before me. I am now also able to turn and share my knowledge and my support with other new families. So, you get to grow in that role from a mentee to a mentor, and it is really special. I think some of the mentor relationships that have been particularly helpful to me, outside of my son's rare disease, are with the local groups that help you understand how to navigate your local school system, your state waiver programs, and your state support services. It makes me feel a little angry that every single rare disease child in the country is seen by doctors and pediatricians, but we are not receiving that information about how to apply for our state waiver programs or how to apply for our state support services or the benefit systems for our kids. We are not getting that information from providers, and so you start to hear about it from other families. Then you start to say, "Well, what is this?" Sometimes you can be delayed in signing up for wait lists that you should be on, and it delays the support and services your family can receive. Those mentors who have been through your systems locally before, can turn around and say, "Hey, you need to sign up for this. You need to do this. Here is how I have navigated this before." It is incredibly important.

**Erika Berg (host):**
*It sounds like it is mostly informal, or have you had any type of formal pairing?*

**Marissa Bishop:**
I have not had any formal pairing. There are networks such as Parent to Parent USA. That is a national network that can help you connect to other parents. For me, it has been more informal. I have found that my child's therapists, both physical and occupational therapists, who also serve other families in my community, have been a really good connector. They say, "Oh, I know a mom. Let me ask if I can give you her number." They have been a really great resource to meet people.

***"As human beings we need anticipatory guidance. We crave to know what to expect when something like this is happening. We all probably went out and bought that book,* What to Expect When I'm Expecting, *when we had our first child. When your child is diagnosed with a rare disease, that book does not exist for you. You have to create it and put it all together by yourself."***

**Jennifer Siedman:**
I think what Marissa is bringing up highlights a big gap in our caregiver experience. As human beings we need anticipatory guidance. We crave to know what to expect when something like this is happening. We all probably went out and bought that

book, *What to Expect When I'm Expecting*, when we had our first child. When your child is diagnosed with a rare disease, that book does not exist for you. You have to create it and put it all together by yourself. Go into the bookstore and look at how many books there are about typical parenting, and you will find a plethora of them. We are now hearing more and more stories from rare parents. We can go to places like Courageous Parents Network and listen to stories. We can go to conferences. We can lean on social media and mentorship to help us learn. However, all of that is really about seeking that anticipatory guidance, both medically for our children, and psychosocially and emotionally for the things that we are experiencing. I think one of the things we really need to focus on as a society is teaching people where to go to find it and even giving them the language to know what it is called. I did not know the word anticipatory guidance until I started working with physicians and the people at Courageous Parents Network. Now I think to myself, if I could have had all of that in the beginning, my care experience would have been completely different. If only I had known what to ask for. If we can equip people to be familiar the terminology and ask for the things they need, we help them build that caregiver muscle. I think Marissa brought up a good point about how we have to look in 90 different places to find that guidance. We have to go to schools. We have to go to groups. We have to go on social media. We have to go to a million specialists. It is exhausting.

**Erika Berg (host):**

*Jan, are there models for information sharing, whether it be through a mentorship or just a common source of information that brings everything together? And if so, what impact does having something like that have on caregivers?*

> ***"I believe that anticipatory guidance is not only needed by individual caregivers, but also by the different associations and foundations being launched by caregivers."***

**Jan Domaradzki:**

I would first like to add one comment to what Jennifer was saying. I believe that anticipatory guidance is not only needed by individual caregivers, but also by the different associations and foundations being launched by caregivers. Frequently, the associations that I collaborate with tell me that they have to invent the wheel over and over again. Not only do the parents have to search for all that practical information, but new associations launched by families and parents face the same challenge. It is also a particularly difficult task for them, because while providing care for their children, they must also gather all the information about how associations and foundations work. This is why anticipatory guidance is also important for associations, especially new ones that are being launched by caregivers.

Now going back to your question, there are, of course, several more broad or umbrella organizations. Global Genes, which was already mentioned, is an American organization, but there are many others such as EURORDIS, in Europe. Many of these organizations provide information on how to connect and how to access both medical and practical information. While the focus is often on disease-related information, caregivers frequently need very practical information regarding everyday activities, such as choosing the best type of wheelchair, and physicians are frequently not aware of such information. Guidance and mentorship is very important, although unfortunately most research shows that it is mostly informal. Very few places offer organized mentorship, like Parent to Parent USA. I think this is one of the most important needs for caregivers, parents, and association alike.

**Erika Berg (host):**

*In all of these spaces, people are sharing sensitive personal information. Marissa, what are some of the key factors that go into creating a safe and supportive environment in these settings, whether in person or virtually, so that caregivers feel comfortable opening up and discussing these personal details of their lives?*

> ***"In our group, there is this culture of everybody celebrating everybody. Our moderators do a good job to make sure that if there is a comment that comes across as particularly offensive or harmful, it is addressed right away."***

**Marissa Bishop:**

When I worked in the school system as an elementary school social worker, I would have small groups. We would always start, before we did any work together, by setting expectations and setting norms for the group and understanding how we were going to speak and respond to each other, and what is appropriate and what is not. I think the same thing is important for any spaces where you are gathering families together. You want to provide expectations for how people will be addressed and respected and lay some sort of foundational rules for those interactions. I think that goes a long way in reminding people of the expectations. We also need to reinforce the fact that this is a nonjudgmental place when we are getting together. There is no playbook for how to manage a rare disease. People and families make decisions based on their knowledge, their culture, their experiences, and their situation. As long as no one is being harmed, there is nothing wrong with that. Everybody is trying to take care of their family the best that they can. Coming from a place where everybody understands the expectations and there is no judgment, I think that goes a long way toward helping people feel comfortable. We have this ongoing Facebook support group and I am in there every day and we also have moderators. I have heard horror stories from some other rare disease groups where they are not supported and the moderators do not really step in. In our group, there is this culture of everybody celebrating everybody. Our moderators do a good job to make sure that if there is a comment that comes across as particularly offensive or harmful, it is addressed right away.

**Jennifer Siedman:**
I think Marissa brings up a really good point. Being with others who understand your circumstance can be empowering, but the truth of the matter is that sometimes there is judgment and there is a lack of respect for an individual family's decision or the direction of care they choose. That is really unfortunate, but the reality is that in these social groups it happens. I think one thing that makes Courageous Parents Network so unique, and can make us seem a little more remote than a Facebook group, is that we are both decision- and disease-agnostic. You can come and explore the concepts that you are experiencing, such as how to care for your healthy children or anticipatory grief. We talk about interventions as well, such as how to decide if your child should have a tracheostomy or not. You can listen to different parents or clinicians talking about a topic, and find the one that resonates and helps you make the best decision for your child in an agnostic kind of way. Sometimes it is nice to go somewhere where you see people like you but not exactly like you, if that makes sense.

**Erika Berg (host):**
*Elle, you have a podcast. How did you come to recognize a podcast as a good vehicle for sharing stories and forging connections between rare disease caregivers, and can you share what went into the journey of building your podcast into a successful resource for the rare disease community?*

> ***"You can listen to a podcast no matter what you are doing, as many of us caregivers are often multitasking. I saw it as a way for me to take control of something in this chaotic, rare-disease space. When you have a genetic disorder, there are different emotions and feelings that go along with that and I said to myself that I cannot change the past, but what I have control over is the future and what other parents and families know about this disease."***

**Elle Cole:**
I started podcasting on my own podcast, called the *Cleverly Changing* podcast, as an outlet. Initially, I did not feel like I could send my daughters to school with other kids, and so I started homeschooling them, and I felt like it was a little isolating for me. I love people and interactions, it was a way for me to develop a larger community. It was a podcast where my kids could participate and were able to meet other kids. That is how that particular podcast started, but then I wanted to do a podcast that was more related to my daughter's rare disease, so I partnered with the Sickle Cell Community Consortium. They were very open to help me develop a podcast, which is the *Vitamin SC3* podcast, where we were able to talk to all different types of people about their different experiences. That really resonated with me because I grew up listening to radio. Talk radio was a huge part of my life, and I felt like it was a way to connect with people without judgment, because it is just listening to words. I knew that I had felt isolated at times during my experience, but a podcast can go beyond the four walls of a person's home. We are now a technology-centered society, you can listen to podcasts on your phone and you do not need to carry a boombox or a Walkman. I am really dating myself by saying that! You can listen to a podcast no matter what you are doing, as many of us caregivers are often multitasking. I saw it as a way for me to take control of something in this chaotic, rare-disease space. When you have a genetic disorder, there are different emotions and feelings that go along with that and I said to myself that I cannot change the past, but what I have control over is the future and what other parents and families know about this disease. The *Vitamin SC3* Podcast is broken into several segments. There is a caregiver segment, which I host, and then there is a science portion, a mental health portion, and a social portion, because we, as people, are doing so many different things. We have to celebrate all of it, just like Marissa said. I was able to do that with a trusted group of friends, and it has resonated with my community.

Now there are many different podcasts in my rare disease community, and people embrace them and learn. There is now a new rare disease podcast that I love about gene therapy, hosted by friends of mine. On December 8, 2023, the FDA approved two gene therapies for the sickle cell community, and that was revolutionary, but it came with a lot of trepidation and fear. That particular podcast shares stories from people who are interested in the therapy and the clinical professionals who are involved in making it happen. It really educates the community and ensures that the questions people have are answered. I love that I have been able to see people who have gone through the therapy, both those who have been successful and those who were not. Because there is so much new science and research, but it is not always successful and there are risks. The podcasts are honest about all of it, not just the positive parts. That is what I love about podcasts: you can be open and honest, and that is the beauty of them.

**Marissa Bishop:**
I have been doing community engagement for CDKL5 for a long time now, and I really recognize the importance of having multiple avenues that people can access content. Everyone has different learning styles and different ways they like to consume information. Starting a podcast for our rare disease seemed like a really fresh way to get the word out. Like Elle said, you just hit play on your phone and whether you are doing dishes, folding laundry, drawing up meds, or driving in the car, you can listen anywhere. Other types of content, such as those on social media, are sometimes at the mercy of the algorithm, which determines if they are seen at all. Newsletters can also get lost in people's inboxes that get out of control sometimes. Rare caregivers are busy and life is unpredictable. With a podcast, you can hit play at the hospital, and you do not need to bring anything with you. It is just so easily accessible. What makes it even more meaningful for our community is the feedback we get. I receive messages all the time from caregivers saying, "That really resonated with me. I feel really seen." What is really special is when we have peer caregivers come on as guests. I have gotten feedback from them that their friends and family have been able to better understand them and what they are going through, in a way that they were not able to before. That is something that has been really special.

## Funding rare disease research: Collaboration to accelerate treatment innovation

Funding for rare disease research has traditionally been led by government agencies like the NIH, but there are increasing opportunities for a wide variety of funding mechanisms to play a role in advancing research and therapeutic development. This panel will explore the diverse ecosystem of funders within the rare disease space, including philanthropic organizations, venture philanthropy, impact investors, and biotech developers. We'll discuss innovative funding models such as venture philanthropy and biotech-focused investments, as well as the concept of spillover economics, in which funding in one area of research catalyzes broader benefits across multiple fields. Importantly, we'll examine how these various funders can collaborate and how their combined efforts can accelerate research and development for rare diseases. This panel will highlight the power of partnership, innovative finance, and cross-sector collaboration in building a sustainable and impactful rare disease research ecosystem.

Participants will:

- Hear about the range of funding sources driving rare disease research
- Gain insights into innovative funding models
- Explore strategies to foster collaboration among diverse funders and stakeholders

## Panelists

**James Levine, Ph.D., M.D., M.B.A.**
**Fondation Ipsen, Paris, France**

**Adora Ndu, Pharm.D, J.D.**
**BridgeBio Pharma, Palo Alto, CA**

**Paola Pozzi, M.A.**
**Sofinnova Partners, Milan, Italy**

**Teri Willey, B.A., M.B.A.**
**National Bleeding Disorders Foundation, New York City, USA**

**Erika Gebel Berg, Ph.D.**
**Science/AAAS, Washington, DC; moderator**

## The Conversation

**Erika Berg (host):**
*Today we will explore the diverse ecosystem of funders within the rare disease space, including philanthropic organizations, venture philanthropy, impact investors, and biotech developers. We will discuss innovative funding models, the science behind investment efficiency, and the concept of spillover economics. We will also examine how funders can collaborate and how their combined efforts can accelerate research and development (R&D) for rare diseases. I would now like to take the opportunity to welcome a brilliant panel today. I will give each of them a chance to say hello and introduce themselves.*

**Adora Ndu:**
My name is Adora Ndu. I am the Chief Regulatory Affairs Officer and the Executive Vice President of Portfolio Strategy and Management at BridgeBio Pharma. My background is in pharmacy and law, and I have spent the vast majority of my career in regulatory affairs and drug development, with a particular focus on rare diseases, which have really found a near and dear place in my heart and professional life. That is what brought me to BridgeBio. Bridge Bio is a Bay Area biotech company that is focused on developing innovative treatments for rare genetic diseases. We were founded in 2015. Our first two approvals were in 2021 in the ultra-rare disease space. The first was for a disease known as molybdenum cofactor deficiency (MoCD) Type A, which at the time impacted just 400 known patients globally. That was a challenging development program. We worked very closely with the FDA, leveraging things like external controls to get the treatment available for patients. Most recently, we received our third approval in November of 2024 for another rare condition known as transthyretin amyloid (ATTR) cardiomyopathy. We continue to drive forward in spaces that are difficult and challenging based on the science and the biology. We have a number of late-stage programs that are really trying to establish precedent and new therapies for diseases like limb girdle muscular dystrophy, autosomal dominant hypocalcemia type 1 (ADH1) and achondroplasia.

**Teri Willey:**
My name is Teri Willey. I am the managing director of Pathway to Cures, which is the venture philanthropy fund of the National Bleeding Disorders Foundation. Inheritable bleeding disorders are, by their very nature, rare diseases. So I am working with a small subset of what Adora talked about. We are a venture philanthropy fund, which is very similar to a regular venture fund in that we invest for equity in companies that are developing cures and other solutions to address unmet needs in the inheritable bleeding disorders community. My background has been a combination of venture investing and technology transfer. In general, my vocation has been acting at the interface of for-profit and not-for-profit organizations to ensure that important early-stage life science discoveries are developed for the benefit of the public.



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**James Levine:**
My name is James Levine, and I am President of Fondation Ipsen in Paris. I previously spent three decades at the Mayo Clinic, working in translational research and innovation. I joined Fondation Ipsen several years ago, motivated both by professional experience and personal exposure to rare diseases. At Fondation Ipsen, our work focuses on advancing knowledge, fostering collaboration, and supporting research ecosystems in rare diseases. Through initiatives such as Crossvine Studio, we contribute to academic research, policy analysis, and data-driven approaches aimed at improving the efficiency and sustainability of research investment and accelerating progress toward new treatments.This is an important and evolving discussion, and I am pleased to be part of it.

**Paola Pozzi:**
I am Paola Pozzi. I am a partner at Sofinnova Partners, which is a leading venture capital firm based in Paris, with offices in London and Milan. We have a clear focus on investing in life sciences. We have seven dedicated strategies that are investing across all the value chains, so starting from early stage to later stage investments. As of today, we manage over €4 billion in assets. I am a partner in one of the early-stage funds, which is dedicated to investing in Italy to create and grow companies that can become global players. There is a specific focus on investing in genetic and rare disorders, thanks to a strategic partnership we established with Fondazione Teleton when we launched the fund in 2018. Fondazione Teleton is a very well-known charity in Italy that has proven to be very successful in supporting basic, translational and clinical research in the rare and genetic space. Many of the programs and products that they have supported have been approved and are now on the market. As of today, we have invested in 10 companies and we are proud to have a company with clinical-stage programs in inherited retinal disorders, showing good safety data and preliminary evidence of efficacy.

**Erika Berg (host):**
*I would like to put the first question to Teri, but everyone is welcome to add their thoughts. At a high level, what kind of trends are you seeing in research activity, drug development, and clinical approvals for drug developers working in rare diseases?*

> ***"We are seeing accelerated growth with rare disease R&D as well as product development in the U.S., but even more so in Europe. There are currently over 10,000 rare diseases, but only about 5% have an FDA-approved therapy, so there is room for new curative therapies and approaches to addressing these unmet needs in the market."***

**Teri Willey:**
We are seeing accelerated growth with rare disease R&D as well as product development in the U.S., but even more so in Europe. There are currently over 10,000 rare diseases, but only about 5% have an FDA-approved therapy, so there is room for new curative therapies and approaches to addressing these unmet needs in the market. We are also seeing, very importantly, an increase in patient involvement. Patient-centric approaches, including opportunities to do decentralized trials, are so important when you are dealing with small populations so you can meet them where they are to ensure they can participate in these studies. All of that is very important, and we are seeing organizations, like Fondation Ipsen, NORD, Every Life, as well as disease-specific foundations like the National Bleeding Disorders Foundation, that I work for, working together to make sure that government incentives continue to support efforts to address these unmet needs. So there are a lot of good things going on, including an increase in understanding the molecular biology and how these diseases work, which makes a big difference. However, we have to be cognizant of the cost. We have seen some life-changing developments in gene and cellular therapy, but we have also encountered some challenges in addressing payer issues to make sure that these really innovative approaches can continue to change lives.

**Adora Ndu:**
I would add that, from the regulatory perspective, one of the trends that we are seeing is continued focus on advancing treatments for rare diseases. When you look at the approvals coming out of the Food and Drug Administration (FDA) over the last couple of years, rare diseases have outpaced approvals for novel products. That is promising and our hope is that we continue to see that trend moving in the right direction, because it is so important. Similarly, when you look across the pond to the EU, we continue to see those trends progressing. I know we are going to touch on this, but there is clearly an evolution in the regulatory and legislative environment as well, which is an important trend for drug developers right now. We are trying to navigate this as we try to advance some innovative clinical trial designs and work on aligning with health authorities on drug development, initiating clinical trials, determining the regulatory path forward, and ultimately getting these products approved for patients. So that is another trend that we are navigating.

> ***"With individualized medicine also becoming a mainstream concept, this is probably the most exciting and dynamic time to be in the rare disease space."***

**James Levine:**
I agree with what has been said. What is particularly striking is the pace of change in the rare disease field. After a period of rapid growth in venture funding, the landscape has clearly recalibrated. At the same time, we are seeing the emergence of new scientific platforms, more adaptive trial designs, and the increasing use of data-driven and computational approaches. Taken together, these developments have the potential to improve how research is conducted and how treatments are developed for conditions where unmet need remains substantial. As more individualized approaches to medicine move into routine practice, rare diseases continue to be an important area for innovation, collaboration, and learning across the wider biomedical ecosystem.

**Erika Berg (host):**

*Paola, can you share with us your take on the current state of public or government funding for rare disease research and therapeutic development relative to other disease areas. What are you seeing?*

**Paola Pozzi:**

I can tell you what Fondazione Teleton has been doing over its 30-year of history in Italy, as an organization solely dedicated to supporting translational research in rare and genetic disorders. They have invested over $740 million, specifically dedicated to translating this research. As I mentioned earlier, they started investing at the preclinical and translational stages, and then they went on to support most of the clinical trials that were then approved by the European Medicines Agency (EMA). For instance, Strimvelis is the first ex vivo gene therapy approved in Europe, and that was in 2016, when the field was still very immature. What Italy has, however, is a strong excellence in advanced therapy development. They work with top scientists that are world-renowned, who, over time, have built not only the basic and translational research capacity, but also all the clinical expertise needed to translate these research programs into products that have been approved and are now available for patients. This charity has been able to do impressive work over the years, through its strong dedication to quality, research, and supporting the best of Italian excellence in this field, and it has really paid off. This results in products that are now available to patients. Strimvelis, for instance, has treated over 45 patients so far. It is indicated for a very rare disease, but the success of this story has also enabled Fondazione Teleton to move more and more products forward. So that is a fascinating story. I am saying this because, before joining Sofinnova Partners and becoming an investor, I spent 14 years in technology transfer in academia. So I have seen this progress firsthand. I was actually in a very prestigious research university hospital at that time where I saw these programs moving from translational work in the lab to the clinic, or the bedside. It has been a really tremendous effort that turned out to be successful. There are a number of products that are now moving towards approval, while Strimvelis and Lenmeldy, another therapy for metachromatic leukodystrophy (MLD), already have an approval. I think this is only the beginning, but these are success stories that we should highlight and be proud of.

**Erika Berg (host):**

*Any regional differences that we should point out that are different from that experience?*

**Adora Ndu:**

I would add that, historically in the U.S., there have been several mechanisms and tools for federal funding to advance research and development. In the last eight months or so, there has been more uncertainty introduced in that space, especially in terms of funding coming out of the NIH to academic institutions. What I would say is for a company like BridgeBio, when we were founded in 2015, this type of funding was at the core of our ability to identify new compounds. We had a team of, what we called "drug searchers". They were essentially going from institution to institution, meeting with researchers, understanding the science behind novel compounds and the biology of disease, and identifying potential collaborations. So we established a number of collaborations with many academic institutions many years ago. In more recent terms, there have been some disruptions to the funding coming out of NIH, especially to different research institutions. We continue to watch that space to see the progress there and where things land. As far as FDA is concerned, there are a few tools that are available. FDA does issue orphan drug grants, primarily focused on natural history studies. Those are, to my understanding, not impacted to date so we hope that they continue. We also have Advanced Research Projects Agency for Health (ARPA-H) that has their funding programs and the work that they do is very important in the rare disease space. We are hopeful, because a lot of this research is important. It usually feeds into ongoing development that other companies, such as BridgeBio, can then come in and help advance and bring to the finish line. So there is a significant role that federal funding plays. I think we probably have to start to think about novel approaches. Maybe it is more of a public-private approach to funding rare disease drug development. I am sure we will talk about that in detail shortly, but there are certainly regional differences that we should be conscious of.

***"We are also encouraged by seeing some foundations step up to address some of the unmet needs in funding because our investments are often in very early-stage companies. Many of them are university or teaching hospital spinouts. So the loss of that type of funding is notable."***

**Teri Willey:**

We are also encouraged by seeing some foundations step up to address some of the unmet needs in funding because our investments are often in very early-stage companies. Many of them are university or teaching hospital spinouts. So the loss of that type of funding is notable. One of our companies recently received an award from Wellcome Leap, from the U.K. Wellcome had put together a £600 million program for addressing unmet needs in certain areas. One of those areas was in bleeding disorders and heavy menstrual bleeding as a real issue and as something that we need to better understand, as an indicator in women's health. So it is exciting to see these types of foundations stepping up, across the world, to focus on areas with unmet needs and to explore how to leverage the good work that is already underway.

**James Levine:**

I would add a European perspective. At the policy level, rare diseases are recognized as a priority in several European countries, including France, with comparable attention in other Member States. This is reflected at the European level through coordinated initiatives designed to strengthen collaboration, data sharing, and translational capacity across borders. It is important to remember that rare diseases are inherently international, given the small and geographically dispersed patient populations. As a result, international collaboration is not optional but essential. That

spirit is reflected in discussions such as this one, where support from public funders, philanthropic organizations, and research agencies across regions contributes to a more connected and resilient research ecosystem. In that context, sustained collaboration between communities—across disciplines, sectors, and geographies—remains a critical enabler of progress.

**Erika Berg (host):**

*Adora, I think you addressed this briefly, but can you talk more about the regulatory environment in this space and how agencies like the FDA or the EMA are incentivizing and prioritizing the development of drugs for rare and orphan diseases?*

**Adora Ndu:**

I will start with the EMA since it is probably more straightforward at the moment. The EMA has always incentivized drug development for rare diseases, and they continue to do so. For example, there are two pathways that I would like to highlight: conditional approval and exceptional circumstances. Both essentially recognize that there will be limitations in the data sets that are submitted for rare disease drug reviews and approvals. These pathways continue to be used, and I think there have been a number of first-in-disease approvals that have gone through them, that have allowed for those treatments to become more broadly available to patients. In the U.S., the FDA, has historically navigated this in a different way and continues to do so. I would say that the FDA is going through a natural evolution, given the change in leadership and the changes in internal structures within the agency. Externally, we are observing and waiting to see where things settle. In general, if we are reading the tea leaves at this time, what we can say is that there is interest and focus in continuing to advance, support and incentivize rare disease drug development. For example, the FDA rolled out the Rare Disease Hub in 2024, which is essentially an infrastructure within the agency aimed to help increase consistency across review divisions and offices, as that was one area of concern that companies were facing. More recently this year we have seen a few things announced. There was a JAMA article, published a couple of months ago, that was penned by the new commissioner of the FDA. One of the things that he talked about was trying to establish this new pathway for rare diseases via a plausible mechanism. So that is something that we will continue to watch. A couple of months ago they also announced this new voucher program, called the Commissioner's National Priority Voucher Program. What that program will do is expedite review and approval. So possibly products could be approved as early as one to two months after the package is submitted, which is pretty significant if we are able to accomplish that, especially as you think about net present value (NPV), funding and return on investment (ROI). All of these things are directly relevant to this new Commissioner's National Priority Voucher. Now the voucher has not been rolled out specifically for rare diseases, but it does include rare diseases. One of the priorities that have been laid out is addressing a high unmet need. And so, to the extent that these new and innovative products are addressing a high unmet need or represent a significant shift in innovation to treat a particular disease area, they could potentially leverage this voucher to make the treatment available much sooner for patients. More recently, just a matter of days ago, there was a new pathway announced called Rare Disease Evidence Principles, which focuses on very rare diseases, so those affecting less than 1,000 patients. For diseases within that space, a developer would be able to submit an application to FDA. Essentially, what that does is that it allows the agency to collectively recognize that more streamlined, flexible approaches should be applied to this product for this disease. So, for example, this could mean leveraging a single adequate and well-controlled study, plus confirmatory evidence, plus novel biomarkers, and potentially a limited data set to establish the standard of substantial evidence for approval. And so while the packaging of this new incentive that has been rolled out is currently available, my sense is that they are trying to establish a process that makes it easier so that sponsors do not have to receive mixed feedback depending on who is reviewing the product and where it lies. Once you have this designation, you should be able to leverage this. So I think it is a signal saying that they are focused on rare diseases, they are interested, and they are trying to roll out a few incentives for development in this space.

**James Levine:**

I was struck by something Adora mentioned. In our work in the U.K., including analytical engagement around the MHRA's innovation initiatives in rare diseases, we have looked at how regulatory approaches can influence the broader research and development environment. Beyond supporting individual programs, there appear to be wider system-level effects in terms of attracting activity and encouraging innovation. I would be very interested in your perspective on how important a predictable and enabling regulatory environment is for helping promising therapies progress efficiently toward patients.

***"A lot of these rare disease therapies are being developed by very small biotech companies, many of them with only one product under development. It is critical for them to be able to engage with health authorities like MHRA, EMA, and FDA and receive reasonable feedback for pragmatic drug development."***

**Adora Ndu:**

I think it is absolutely critical. The ability for developers to have certainty in the regulatory process, so they can develop their treatments through the most streamlined and efficient drug development pathway possible, and make those treatments available to patients, has tremendous spillover economic benefits. A lot of these rare disease therapies are being developed by very small biotech companies, many of them with only one product under development. It is critical for them to be able to engage with health authorities like MHRA, EMA, and FDA and receive reasonable feedback for pragmatic drug development. That way they can continue to exist and they can actually see their product through to approval, get it to patients, generate revenue, and then continue to expand their development into other areas and other diseases. So it is absolutely critical.

**Erika Berg (host):**

*Let us now talk about some of the funding models that help bring these life-saving medications to market. Teri , to what extent are you seeing dedicated venture capital funding in support of commercial development of new therapies for rare diseases, and how has this activity been changing in recent years?*

**Teri Willey:**

Well, we are very lucky to have Adora's fund among us. Unfortunately, this is not the norm, but it is wonderful to have this type of expertise and smart money in an investment involving a rare disease. What I am seeing are more and more disease-specific foundations enlarging or launching for the first time venture philanthropy funds, and certainly the National Bleeding Disorders Foundation is an example of that. We only launched in 2023, so we are a newcomer in that regard. Part of the contribution to the mission in doing that is to say there are a lot of solutions out there in research laboratories and in early-stage biotech companies. Some of them are specific to our community in bleeding disorders, and some of them are really amazing platforms that could be applied to our patient population. The question is: what would it take for them to move these solutions off the back burner and into their pipeline? What do they need? Oftentimes it is money, but often it involves understanding the patient population. We call them lived-experienced experts. Sometimes it is just about understanding the nuances and the biology of the disease and then having the capability to syndicate, to find other people to co-invest with and establish a strong investment case, in order to bring these ideas to the public and patients in a meaningful way. So we are seeing more disease-specific foundations. We are seeing top-tier and traditional venture funds participate in these rounds, especially when there is a platform involved. In our case, some of our indications might not be their big winner, but they can be very powerful clinical proof of principle, to show that the platform has legs and could lead to impacting the health of even larger populations. That is something that is really exciting. I am starting to see, and this may just be wishful thinking on my part, a continued involvement, and perhaps an increased involvement, from sophisticated family offices across the world that have an interest in rare disease. The challenge is figuring out which ones are interested and doing that kind of matchmaking because there is not a straightforward way to do that. So there is hope in having lots of different varieties of funding along with experienced people, funds and entrepreneurs coming together to put those types of funding rounds together in a way that makes sense, aligns interests, and helps these companies get to the finish line with their product development.

**Erika Berg (host):**

*Paula, you are part of a dedicated program focused on the commercialization of rare disease research from the Telethon Foundation. Can you tell us more about how that program works and how such a design can accelerate the clinical translation for therapies that are rooted in promising academic research?*

***"We are an early stage fund, so what we do is pick technologies with breakthrough potential developed in academia and we build companies around them. So we have to be very focused in identifying what we truly believe is a breakthrough therapy with a potential to become a product for rare disease patients."***

**Paola Pozzi:**

I am going to build on what Teri just said because I am in full agreement with it. We are an early stage fund, so what we do is pick technologies with breakthrough potential developed in academia and we build companies around them. So we have to be very focused in identifying what we truly believe is a breakthrough therapy with a potential to become a product for rare disease patients. It is quite difficult, because we have to invest early and when we invest, we typically invest at the seed stage. This can be from a couple of million up to four million, for a seed investment. We have to make sure that these seed investments can grow the company and attract dedicated funding, so that the programs actually reach clinical proof of concept. So that is really the challenge for us, as a venture fund focused on early-stage investments: being able to select opportunities based on quality and what we believe is the best science available, while making sure that what has been done and promoted at the academic level can be translated into entrepreneurial and industry settings.

It is a long journey, and I am saying this because I am mostly focused on investing in advanced therapies because, as I mentioned, Italy has a renowned excellence in this field. We therefore know that these are highly capital intensive investments. So, when we decide to make an investment, we set a high bar. At Sofinnova, we always say that we invest not only in science but in the right team. The team behind the project is crucial, so the early developers in academia, but also being able to develop the right team that is successfully translating to the clinic. I am talking about the regulators and managing all the CMC (Chemistry, Manufacturing, and Controls) efforts behind the programs that need to be further supported, and having the right managerial experience to bring these companies forward and ensure successful clinical translation.

**Erika Berg (host):**

*James, we talked about how rare disease research can produce spillover benefits in terms of those beyond the direct benefit to any one patient community in domains such as technology development or biological knowledge. Can you talk about these effects and how they can amplify the impact of an R&D investment in rare disease research?*

**James Levine:**

I think there has been an evolution in how we understand spillover effects in rare disease research. Early on, spillovers were often discussed primarily in market terms—whether insights from a rare condition might later be applied to more common diseases.

While that remains relevant, the concept has matured and broadened. Today, spillovers are increasingly associated with shared platforms, methodologies, and infrastructures, such as enabling technologies, data generation, and approaches to evidence development that can be applied across multiple rare diseases. In this sense, spillover value is not only about market expansion, but also about improving access, reducing development costs, and accelerating timelines. Importantly, spillovers are no longer purely economic. Advances in areas such as data science and computational methods have the potential to support more efficient therapeutic development across diverse disease areas. As these approaches continue to evolve, they may play an important role in shaping more sustainable and responsive therapeutic ecosystems.

**Adora Ndu:**
I could not agree more. When I think about development and the regulatory space, quite often the spillover is certainly there. It is what we saw in the field of oncology, with a lot of innovative approaches within the oncology space. Similar conversations are now happening when we look at rare diseases and what we can take from rare diseases and apply to more common diseases with regards to some of the trial designs, development of novel biomarkers, use of a single adequate and well-controlled study and what level of data should be sufficient, and the role of confirmatory evidence in those instances. So we are certainly seeing that and the ultimate impact of that is it streamlines drug development. It reduces costs of drug development. It reduces the time of the end-to-end cycle of development from the non-clinical to clinical and, ultimately, to commercialization.

**James Levine:**
I would add that improving the efficiency of therapeutic development has the potential to influence affordability over time. Cost remains a significant barrier to access in many health systems, and this is particularly relevant in areas of high unmet need. For that reason, discussions about investment incentives, efficiency, and sustainability are not abstract; they are closely linked to questions of access and long-term impact. These are important considerations as the field continues to evolve.

**Erika Berg (host):**
*Teri, as an investor, what are some of the key considerations that you look for when bringing a potentially promising rare disease startup into your portfolio?*

**Teri Willey:**
The considerations are traditional venture considerations for the most part. We invest like a traditional early-stage life sciences investor in many ways. We want to make sure that the idea is solid and the team is solid or we can attract the team to the company. I think the way that we differ is that we are narrowly focused on inheritable blood and bleeding disorders. We do not have a traditional venture structure, in that we do not have traditional limited partners that we share returns with. We are an evergreen fund and our funding comes from donors. So any equity realizations or returns on our investment go back into the fund for reinvestment and to support our community. That is one way in which we are different. In order for the companies we invest in to be successful, they must have a strong investment case for traditional investors, and follow that best practice. I think that is very important. The way that this fund is different than the other types of investing I have worked in is that we put a very heavy emphasis on the front end, so on science and clinical evaluation. We have an amazing scientific advisory group made up of key opinion leaders, mostly from the U.S., but also from around the world, in the field of inheritable blood and bleeding disorders. They are available to us as volunteers. We meet at least monthly, and usually more often, to review specific opportunities. This is proving to be extraordinary in terms of the insights we can gain and the advice we can give back to the companies as well, because we want them all to be successful, whether we invest in them or not. Then we move on to our traditional investment committee and the development of an investment memo and investment case. So even though we are a venture philanthropy, we are only successful if we can build the strong investment case that attracts syndicate partners.

***"I think that being aligned with the needs of patients is the most powerful funding mechanism imaginable."***

**James Levine:**
Teri, I think you have highlighted an important point: venture philanthropy should be understood as a complementary, and often highly effective, approach to supporting therapeutic development. In disease-focused settings, it brings deep domain expertise and sustained engagement with patient communities, which can be especially valuable in shaping research priorities and development strategies. Alignment with patient needs is a defining strength of this model, and patient perspectives are increasingly recognized by regulators as an important part of the development process. In that sense, venture philanthropy has demonstrated how mission-driven investment can play a meaningful role alongside more traditional funding approaches in advancing treatments for rare diseases.

**Erika Berg (host):**
*Are there any other important ways in which venture philanthropy differs from traditional approaches to venture capital and other venture funding models?*

***"What you see is that venture philanthropists are less worried about an early stage molecule or biologic not making it. They are much more committed to whether this has the potential to impact the patients receiving cures. It is that strong commitment to patients that I think is what differentiates venture philanthropy from true venture capitalism."***

**James Levine:**
One of the distinguishing features of venture philanthropy is the centrality of patient impact in decision-making. In disease-focused philanthropic models, investment choices are often guided as much by potential benefit to patients as by traditional measures of technical or financial risk. Experience across multiple initiatives suggests that this orientation can support a different, but not necessarily riskier, approach to early-stage development; one that prioritizes long-term impact and sustained engagement over short-term outcomes. As the governance and professionalization of venture philanthropy have continued to mature, it has emerged as a credible and complementary mechanism within the broader innovation and funding ecosystem for rare diseases.

**Teri Willey:**
One of the common themes that emerged as we were looking at our pipeline of companies, having met with about 220 companies since we launched, which is a small number compared to the throughput in traditional venture funds, was that they were late in engaging patients. We saw this particularly with companies that were already into the clinic or getting ready to launch their first human studies. Because of that, there were certain nuances in the study design that could have been corrected earlier. What I mean by that is they had put together solid clinical models and study designs sufficient to get them approved by the FDA, but with a product that was not going to be as attractive to the people that they were trying to reach. So they might have an FDA-approved product, but maybe not one that would achieve the market penetration that they hoped for, to put it in business terms. So one of the things that has been very important to us is to continue to engage patients earlier and earlier. Even when we are not investing, we advise companies by putting our virtual advisor groups together with patients to ensure they are considering these nuances because they are critical to their success. This approach is highly synergistic, helping companies reach patients more efficiently and sooner.

**Paola Pozzi:**
I fully agree with what Teri just said. We are seeing the same in our portfolio company. Engaging with patient advocacy groups and patient associations earlier, and recognizing the benefits of doing so, is vital to successfully translating these products to the clinic.

***"Because when you speak with companies, it is fascinating how many drugs for very rare diseases are shelved. They are sitting on shelves across many companies and academic institutions, primarily because of funding. So the mechanism to take these products off the shelf, including bringing together funding, with venture philanthropy being one of the key areas for advancing these treatments, represents a huge opportunity. I think these conversations need to continue so that the products that were shelved, not due to a lack of solid science but due to a lack of commercial viability and therefore inadequate funding, can be taken off the shelves and put into the hands of patients."***

**Adora Ndu:**
I would agree that in both the for-profit as well as the non-profit model it is critical. At BridgeBio, the patient voice is at the core of every decision we make, even as a for-profit company. It is critical at early, middle, and late stages. So when we are doing some exploratory work to identify different conditions that we would like to pursue in research and development, we are speaking with the patient community. When we are developing the protocols, we are speaking with the patient community. When we are engaging with regulators, we are speaking and involving the patient community throughout that process. One thing I wanted to build on with regards to the venture philanthropy discussion was that I think that this is critical, especially in the ultra-rare disease space. These are the diseases where the commercial viability is limited or nonexistent. So for the products that are either NPV neutral or marginally positive, thinking about the innovative funding models that could enable products that have solid science to continue to advance is important. There is a sort of groundswell happening right now, with different groups looking at this very carefully. We have been involved in a number of conversations to explore what can be done to help enable this conversation and create some actual traction. Because when you speak with companies, it is fascinating how many drugs for very rare diseases are shelved. They are sitting on shelves across many companies and academic institutions, primarily because of funding. So the mechanism to take these products off the shelf, including bringing together funding, with venture philanthropy being one of the key areas for advancing these treatments, represents a huge opportunity. I think these conversations need to continue so that the products that were shelved, not due to a lack of solid science but due to a lack of commercial viability and therefore inadequate funding, can be taken off the shelves and put into the hands of patients.

***"There is a real groundswell of interest right across this space and there are multiple alternate mechanisms of funding which are becoming more and more interesting. I think venture philanthropy has led the charge in this regard, but you also have social impact bonds, crowdfunding (which is very relevant to patient groups), and collaborative consortia."***

**James Levine:**
I agree. One area of interest for us has been the idea of aggregating or coordinating assets and initiatives, with the aim of creating more sustainable development pathways across multiple rare diseases. Rather than focusing on single programs in isolation, this kind of approach can help align resources, expertise, and incentives in a way that supports broader patient communities. We are also seeing growing interest in a range of complementary funding mechanisms, including venture philanthropy, collaborative consortia, and other mission-driven or policy-enabled models. Taken together, these approaches reflect a wider effort to place patients more centrally within research and investment decisions. In that context, rare diseases continue to serve as an important testbed for more individualized, patient-focused approaches to innovation, with lessons that may inform the wider health ecosystem over time.

**Erika Berg (host):**

*Paula, given the small number of patients for a particular medication, what are some strategies that make taking on such a risk more compelling to investors?*

> ***"We have to build investment cases that are strong, while making sure that we have all the enabling elements in place to make these products affordable to patients."***

**Paola Pozzi:**

I think we need to make sure that we are implementing efficiently and optimizing all different strategies. We have been talking about philanthropy and venture capital investments. We have to build investment cases that are strong, while making sure that we have all the enabling elements in place to make these products affordable to patients. It is a really long cycle, but we have to make sure that all the key players are working together to make these products available to patients in an efficient way. I am also thinking about the fragmentation that there is in this environment. We need to work together to avoid fragmentation, for example, at the regulatory level, while also streamlining operations and improving efficiency in clinical translation, so including all the expedited pathways that were mentioned earlier. Importantly, we also need to consider the cost of goods for these therapies, especially in advanced therapies, as they heavily affect their adoption by patients.

> ***"Above all it comes down to quality, capacity, and capital efficiency. As investors, we have to ensure that the product being delivered at the end of the day becomes sustainable for the health system."***

I believe it is a combination of factors, but above all we have to make sure that we are investing in high quality and that we are supporting the translational research moving forward. I would also like to mention the importance of improving the diagnosis of these patients, because there are so many undiagnosed patients out there. If we are able to improve the diagnosis, by using artificial intelligence that James mentioned earlier, we can increase the number of patients that can actually benefit from these therapies. What I am saying is that there are a number of factors that we need to align to make sure that we are streamlining the approval process for these therapies. Above all it comes down to quality, capacity, and capital efficiency. As investors, we have to ensure that the product being delivered at the end of the day becomes sustainable for the health system.

> ***"The economic consequence is straightforward: if you can better de-risk, investments are more efficient, which brings more investors to the table, and ultimately you can have cures much more quickly through simple financial structures. "***

**James Levine:**

I agree. One important point that is sometimes left implicit is the role of risk itself in shaping outcomes in rare disease development. As in many areas of biomedical research, attrition rates are high, and this makes efficiency and risk management particularly important considerations.

There is growing recognition that improving how risk is assessed and managed, through better data, more robust early evaluation, and coordinated approaches, can help make research and development pathways more sustainable. In that sense, de-risking is not about eliminating uncertainty, but about making more informed decisions earlier. Ongoing work across the field, including collaborative analyses and shared methodologies, suggests that advances in data availability and analytical tools may further support these efforts over time, with potential benefits for both investors and, ultimately, patients.

**Adora Ndu:**

I completely agree. To build on what has already been said, starting with solid science is foundational. The compound must be strong from a safety and efficacy perspective and demonstrating proof of concept through the clinic is critical. I think that is foundational for any product development and for being able to take that forward and ensure that you have the ROI. I also want to expand on the efficiency piece. Efficiency is crucial in two areas: operationally and in research and development. Efficient research and development really looks like pragmatic drug design, expedited clinical trial recruitment, being able to initiate your trials very quickly, and being able to think through innovative approaches to actually speed up the drug development. That requires a little bit of foresight and rigorous negotiation with the agency to really align on what is essentially the basic requirement or the minimum data set that is required in order for us to understand and have confidence that this treatment is safe and effective so that we can advance that forward. On the operational side, efficiency is one of the areas, in addition to science and patient engagement, that BridgeBio has worked on to optimize.

That is, at the core, another foundational pillar of our organization because we are a hub and spoke model. We have our central organization, our central services, which is where we have a few of the shared services. Then we have smaller companies that we have spun out. Each of those companies is focused on driving and executing the development of specific program areas. They are lean teams, they are experts, and they are focused on executing. This structure allows us to spread risk across the organization because each of these companies is focused on distinct disease areas. We are able to pull in experts within each of these smaller companies and the benefit is that if one product does not make it to a certain milestone, it does not impact the rest of the portfolio and the rest of the organization. So from a de-risking perspective, that is also one of the core areas that we are focused on. We actually published an article in 2024 in the Journal of Portfolio Management where we talk about the model that BridgeBio has leveraged and established to move very quickly and minimize risk, with a very lean operating infrastructure.

**Erika Berg (host):**
*Are there other innovative funding models that you see emerging that could meaningfully move the needle in terms of accelerating rare disease drug development? I would love it if everyone took a turn sharing their thoughts.*

***"Finally, we need to avoid the fragmentation among the different systems, because at the end of the day, we are all doing this work for the benefit of patients."***

**Paola Pozzi:**
The funding model itself needs to look at return on investment and building a really strong investment case. What I liked about the conversation today is how we also highlighted the importance of leveraging, for example with platform technologies, so taking the lessons from one product and applying them to another and making this process more efficient. What I would very much encourage is platform-expedited designation programs that are more and more facilitated and put into practice. I would also like to see other models that are also efficiently sustaining and helping companies to be capital efficient. The priority revenue voucher, for example, is a great benefit to whoever is developing these kinds of drugs. I think that what we have to make sure of is that we combine and have access to different funding opportunities. It is not venture capital alone that can solve the problem. It is a combination of factors and it is essential to have a streamlined regulatory framework that really enables this efficiently. Finally, we need to avoid the fragmentation among the different systems, because at the end of the day, we are all doing this work for the benefit of patients. So, it does not really matter who is doing it. As long as we are maintaining the quality and making this an efficient process, it should work out.

**James Levine:**
It does feel as though several important developments are coming together in the rare disease space. Advances in scientific platforms, data-driven approaches, evolving regulatory frameworks, and more thoughtful approaches to risk are all influencing how research and development is carried out. Taken together, these trends suggest a moment of meaningful opportunity for the field, and forums like this are valuable for examining how they can be aligned responsibly to support progress for patients.

**Teri Willey:**
At the end of the day, it still takes people to coordinate all of this, to line it up, and make sure that all the smart people play nice together so we can make this happen. I think that is very important. One group that we are grateful to is LaunchBio, for doing that kind of matchmaking between rare disease startups and investors and now, more increasingly with family offices as well. Despite all of the new technologies and innovations that we have, it still takes people to pull it all together and make it happen.

***"We see a lot of families that are really searching for treatment for their disease or their child's disease. You even see families and parents becoming drug developers because nobody else is doing anything in that space. As a result, there are many small companies that have been established by families. I think there is an opportunity to think about how to enable research in that space, where no research is currently happening. Establishing a federal fund dedicated to ultra- rare diseases, where there is no commercial viability, could help advance these forward."***

**Adora Ndu:**
Paola, I heard you mention the priority review voucher, which I think is a critical and a much appreciated incentive for drug development in the pediatric rare disease space. As we all know, it was not reauthorized. We are waiting very patiently to see if it will be reauthorized because that voucher has proven to be a lifeline for many developers that are in the rare disease space. For our first approval, we received the priority review voucher, we sold it, and we were able to redistribute the revenue across other development areas to continue drug development in this space. So it is critical. The second point that I would add on the wish list, is the role that a federal fund could play in the ultra-rare disease space, where no commercial development exists. We see a lot of families that are really searching for treatment for their disease or their child's disease. You even see families and parents becoming drug developers because nobody else is doing anything in that space. As a result, there are many small companies that have been established by families. I think there is an opportunity to think about how to enable research in that space, where no research is currently happening. Establishing a federal fund dedicated to ultra-rare diseases, where there is no commercial viability, could help advance these forward.

## Humans and AI collaborating to solve rare disease challenges: Opportunities and pitfalls

Artificial intelligence (AI) has become an essential tool in the fight against rare diseases, offering transformative potential in areas like medical diagnosis, drug discovery, and insurance claims processing. By harnessing the power of AI, researchers, healthcare providers, and organizations are making strides in overcoming the unique challenges posed by rare diseases, such as delayed diagnoses, limited treatment options, and barriers to health care access. However, while AI offers numerous opportunities, it also presents risks and limitations that must be carefully navigated. This panel will explore how AI is being integrated into rare disease care and research, discussing its applications in analyzing medical records to assist in diagnoses, accelerating drug discovery, and evaluating insurance claims. Panelists will also address the potential pitfalls of relying on AI, such as algorithmic bias, data privacy concerns, and the need for human oversight to ensure accuracy and fairness. The discussion will examine the delicate balance between leveraging AI's power and ensuring that the human element remains central to decision-making in rare disease care.

Webinar participants will

- Learn how AI is currently being applied to rare disease challenges such as diagnosis, drug discovery, and insurance claims.
- Gain awareness of the risks and limitations of AI in rare disease contexts, including bias, privacy, and equity concerns.
- Be able to recognize the importance of maintaining human oversight to ensure fairness, accuracy, and ethical decision-making when using AI in rare disease care and research.

## Panelists

**Danton Char, M.D.**
**Stanford University, Stanford, CA**

**Tim Guilliams, Ph.D.**
**Healx, Cambridge, England**

**Sherri Rose, Ph.D.**
**Stanford University, Stanford, CA**

**Chunhua Weng, Ph.D.**
**Columbia University, New York, NY**

**Erika Gebel Berg, Ph.D.**
**Science/AAAS, Washington, DC; moderator**

## The Conversation

**Erika Berg (host):**
*Today we will explore how AI is being integrated into rare disease care and research, discussing its applications in analyzing medical records to assist in diagnoses, accelerating drug discovery, and evaluating insurance claims. We will also address the potential pitfalls of relying on AI, such as algorithmic bias, data privacy concerns, and the need for human oversight to ensure accuracy and fairness. The discussion is going to examine the delicate balance between leveraging AI's power and ensuring that the human element remains central to decision making in rare disease care. I would now like to take the opportunity to welcome a brilliant panel and give each of them a chance to say hello and introduce themselves.*

**Chunhua Weng:**
I am a faculty member in the Department of Biomedical Informatics at Columbia University. My training background is in computer science and health informatics. I have been studying medical records, particularly electronic medical records, and how to leverage them for clinical phenotyping, cohort identification, and knowledge discovery. We have been looking at how to leverage nuanced, large-scale phenotypes in medical records that can be used to drive gene prioritization and rare disease diagnosis.

**Sherri Rose:**
I am a professor of health policy and director of the Health Policy Data Science Lab at Stanford University. My main research focuses on developing and integrating statistical machine learning and AI approaches to improve human health, including methods for rare outcomes. I have a PhD in biostatistics. Within health policy, I work on algorithms in healthcare, including risk adjustment and health program evaluation. Additionally, I teach a course on reproducible research.

**Tim Guilliams:**
I am the co-founder and CEO of Healx. We are an AI-enabled rare disease biotech company from Cambridge in the UK. I am also the co-founder of a rare disease charity called the Cambridge Rare Disease Network; I started those two organizations when finishing my PhD at the chemistry department at Cambridge University.

**Danton Char:**
I am one of the pediatric cardiac anesthesiologists at Lucile Packard Children's Hospital at Stanford. I provide anesthesia for children and young adults with heart disease. My early research looked at the implementation of whole genome sequencing into the care of critically ill children and the ethical issues that came up with that. I have become a medical ethicist in my research and

through that work I have begun to look at big data ethical issues which led to my work on AI. I am now part of Stanford's oversight team for all the AI being considered for clinical rollout across Stanford Healthcare.

**Erika Berg (host):**
*You have all engaged with AI in different domains of clinical research in the healthcare world. How recently have you seen this technology, which still feels new but has become mainstream, and what have been the drivers of this mainstream adoption?*

**Chunhua Weng:**
It has been an exciting time over the past year and a half. We have seen a lot of enthusiasm towards generative AI, ChatGPT, and other large language models. They are being used to extract human phenotype concepts from medical records and then converting these phenotype concepts into ontologies, such as the Human Phenotype Ontology. This enables semantic interoperability across the medical records and other knowledge bases, allowing us to analyze the phenotype-genotype associations. This is very exciting, because right now the ability to use large language models to extract and normalize these phenotypic concepts is reaching a new level. They are achieving better accuracy and better reasoning abilities. We see the enthusiasm among the trainees as well as clinicians and clinical researchers. Everybody is excited about exploring the new opportunities to leverage this new technology for phenotype-driven rare disease diagnosis. In my own lab we are also developing algorithms for phenotype-driven genetic test recommendations for rare disease patients. As many people are aware, it is a long odyssey for rare disease patients to reach a diagnosis. Along the way, they need to go through many genetic tests, many of which are not relevant and can be very expensive. Some of them may not be covered by their health insurance. We look at the rich information in the medical records, particularly the phenotype concepts in their genetic counseling notes and other clinical notes and find out they are actually very valuable for giving recommendations on what genetic tests will be the most relevant for the phenotypic profile of these patients. Our next step involves looking at the economic analysis to see the economic value of these phenotype-driven genetic test recommendations. It is very exciting and we are very happy and optimistic about this new era of using AI for rare disease diagnosis and genetic test recommendations.

**Sherri Rose:**
I think it depends on the research area you work in and what we consider AI. If we are focusing on things like generative AI and large language models (LLMs), over the last few years we have seen a lot of progress in these tools, but a lot of what is claimed to be AI is not what we would have previously called AI. I think that is important to highlight. We used to refer to some of these tools, those that are not large language models, as statistical machine learning or simply machine learning. I think if we are bundling all these tools together, we need to remember the limits of some of these tools, that we need to be aware of, and that we have been here before. So, some people who are newer to the AI space were not here for the previous hype cycles. I think that is something that we should really think about, especially when we are looking at healthcare data, because I have been working in this space for a long time and everything starts with, "AI is going to revolutionize healthcare," and we have been here before.

***"On the clinical side, we have not seen much of a dramatic change in patient-focused care from AI tools. What we have largely seen is patients conducting AI research at home regarding clinical conditions and patients coming into clinic with information provided by AI tools, including ChatGPT."***

**Danton Char:**
I think I have a guarded optimism. On the clinical side, we have not seen much of a dramatic change in patient-focused care from AI tools. Largely what we have seen is patients doing AI research at home about clinical conditions and coming in with information provided by AI tools, including ChatGPT. That is a mixed bag, because one of the things we must do is sort out which of the information they have received at home is relevant to the care that they are pursuing, and that is a challenge. I also agree with Sherri that we went through all of this before with the electronic health record (EHR). There is a great deal of excitement, and I would say many clinicians say that we still deliver healthcare and we have the EHR. I have concerns that it will be the same with AI: that we deliver healthcare and we have AI-enabled EHR tools.

***"What is happening right now is that in drug discovery, the current paradigm is called the target-based paradigm and typically involves a single target. Biology, however, is incredibly complex, with 22,000 genes and more than 60,000 proteins. So, there is an opportunity to now use AI, but also other statistical methods and computational biology, to understand the rare disease biology in a different way."***

**Tim Guilliams:**
We are focused on drug discovery and development. From our perspective, we really see an opportunity and already an impact to understand rare disease biology in a more complex way, where you do not have to dumb down the rare disease biology to a single protein target, for example. What is happening right now is that in drug discovery, the current paradigm is called the target-based paradigm and typically involves a single target. Biology, however, is incredibly complex, with 22,000 genes and more than 60,000 proteins. So, there is an opportunity to now use AI, but also other statistical methods and computational biology, to understand the rare disease biology in a different way. We can then predict the right, in our case, small molecules, that work on that disease and can effectively restore your disease state to a healthy state, but more at a systems level instead of a single target pathway protein

level. I think that is where we see some major breakthroughs, at least preclinically. We now have drugs in Phase 2 clinical trials, and I think within perhaps three to five years, we will have the first AI-discovered drugs reaching approval and the market. So, we are still a few years away from real patient impact.

**Erika Berg (host):**
*Sherri, you mentioned the hype cycle earlier and the significant enthusiasm about what AI can deliver. Are you at all concerned that this enthusiasm and these rapid developments in AI solutions may be outpacing the evaluation of risks and ethical considerations?*

***"When we look at the proliferation of AI articles in healthcare, a recent review found that only 5% of the LLM studies actually used real patient care data. So, this is a significant problem if so many of the studies are looking at small sample sizes with structured text vignettes."***

**Sherri Rose:**
Absolutely. One of the things that I feel very strongly about is that more rigorous evaluations of these tools are needed, which include looking at effectiveness, risks, and ethics. This was previously the mandate, and that was when we were only focusing on whether it was effective. Now, a lot of the time we are not even doing that. Fifteen years ago, when I would develop new machine learning algorithms, the most common refrain was that no one will ever use this. The bar for proving the tool was worthwhile was extremely high, as it should be. I think one idea that I would like to ground in the conversation is that just because a tool exists does not mean that it will necessarily improve health or enhance decision making. Our evaluations really need to focus on multiple evaluation metrics, external data sources, generalizability concerns, as well as data and algorithmic bias evaluation. When we look at the proliferation of AI articles in healthcare, a recent review found that only 5% of the LLM studies used real patient care data. So, this is a significant problem if so many of the studies are looking at small sample sizes with structured text vignettes. A common response that I get to these types of criticisms is that the tools will get better over time. I like to then reply by saying, "Then why would we not wait until they demonstrate superior performance?" Again, that used to be a basic bar, and it is so important in healthcare for us to have a lot of confidence in the performance of these tools.

**Erika Berg (host):**
*Danton, from more of a clinical perspective, I am curious about your thoughts on this. Are we moving too quickly and are we evaluating these tools appropriately?*

***"I think we have now seen several real-world implementations of tools that we envisioned being very helpful to healthcare delivery, yet we struggle to come up with a model where we can pay for them or pay for their use."***

**Danton Char:**
I agree with what Sherri said. I also would call out something that Chunhua had said earlier, which is that we are still working very hard to prove the economic value of these tools. I think we have now seen several real-world implementations of tools that we envisioned being very helpful to healthcare delivery, yet we struggle to come up with a model where we can pay for them or pay for their use. One example would be predictive tools to screen the poorly accessed patient populations for serious diseases, such as diabetic retinopathy. Although there are societal costs saved by preventing disease, it is very difficult to convince health systems to pay for tools for patient populations that are very low reimbursement. This is particularly pronounced if the tools are extremely expensive and the accuracy required to give meaningful care through these tools is very expensive to deliver.

**Erika Berg (host):**
*I feel like we have given a good overview of the current landscape, I would now like to talk more specifically about AI in the rare disease space. Chunhua, your team has been exploring opportunities to apply deep learning and other AI methods to facilitate early and accurate diagnosis of rare diseases, which is a big problem in the rare disease space. What are some of the exciting opportunities you see there, particularly as early-life genomic sequencing becomes more prevalent, and where are we with respect to these tools being used in the clinical decision support system?*

**Chunhua Weng:**
We have been working on this in collaboration with two experts in rare disease research. The first one is Dr. Kai Wang at the University of Pennsylvania and the Children's Hospital of Philadelphia, and the second expert is Dr. Wendy Chung at Boston Children's Hospital who specializes in rare diseases. For almost one decade now, we have been looking into large-scale EHR data and developing a serious algorithm for clinical phenotype extraction from the notes, or EHR narratives. We then use these extracted phenotypes to map them to Human Phenotype Ontology and then to look at how they can be useful for gene prioritization and matching a patient's phenotypic profile to known cases in the literature or in published genotype-phenotype knowledge bases to help with the diagnosis. We also use this extracted phenotype to facilitate a genetic test recommendation, as I mentioned earlier. So far, we have been evaluating this algorithm in a lab setting, essentially using benchmark data sets that are available within the research community. Ideally, what we want to evaluate is the impact on patient diagnosis: how many patients we can diagnose and how much we can shorten the time to diagnosis.

***"With the near-universal adoption of EHRs, the rich phenotypic data they contain will be extremely valuable."***

I think the major barrier there is what the implementation science people have been talking about extensively. For the algorithm to be able to run within the current EHR ecosystem it will involve a significant undertaking. While we work in the academic setting as researchers, EHR systems are usually owned and managed by hospitals and healthcare facilities. For the algorithm to run in a clinical practice setting, we have a long way to go. We have been looking into integrating informatics and AI algorithms into a clinical setting since 2011, and we feel like we have not made a lot of progress. There is still a lot of work that remains to be done. Despite these challenges, however, we remain optimistic. With the near-universal adoption of EHRs, the rich phenotypic data they contain will be extremely valuable. In addition, the newer algorithms, such as federated learning, are likely to play an increasingly greater role. It will enable multiple institutions to collaborate with each other without compromising patient privacy, while still protecting patient data security. This approach enables collaborative rare disease phenotype discovery. One example of our recent work is OARD, which stands for Open Annotation for Rare Disease. In this project, we parsed all the EHR data of about 6.5 million patients at Columbia University, spanning multiple decades, and including a majority of the clinical notes. We also incorporated data from all the patients at the Children's Hospital of Philadelphia. By leveraging these two institutions, we were able to conduct cross validation and external evaluation and build a knowledge graph showing the associations between phenotypes and rare diseases. We are hoping that more initiatives like this will emerge, allowing for the contribution of more data for rare disease research. Through this work we have identified a lot of novel phenotype-rare disease associations that were previously unknown in the literature. The next important step is to develop robust verification methods to determine which of the newly identified associations are truly meaningful and can help us to support earlier and more accurate diagnosis.

**Erika Berg (host):**

*Tim, I would like to talk about Healx, which is somewhat unusual as a drug company, as you are principally focused on targeting rare genetic disorders. Can you talk about how you and your colleagues at Healx are leveraging AI as a tool to accelerate discovery and development of drugs specifically for rare disease?*

***"From a company perspective, whenever we start a new program, we establish partnerships with rare disease foundations and charities in that specific area. This is because they are the true rare disease experts: they understand the unmet needs, they help us access missing data models, and they help us generate the required data that we need in our algorithms."***

**Tim Guilliams:**

We are an AI-enabled rare disease biotech and there are two important components to our approach. Basically, we are rare first and AI first, but we think about AI in a broader sense. What is so great about this panel today is that everyone is trying to use AI to do something positive for the world, such as helping rare disease patients. The opportunity to use the latest tools to have a positive impact cannot be overstated. From a company perspective, whenever we start a new program, we establish partnerships with rare disease foundations and charities in that specific area. This is because they are the true rare disease experts: they understand the unmet needs, they help us access missing data models, and they help us generate the required data that we need in our algorithms. We also hire rare disease parents to help drive projects forward. I think this is incredibly valuable, and I will share an example in a moment. From an AI, machine learning or computational biology perspective, we are focused on first understanding the complex rare disease biology. Typically, there is no validated target for a rare disease. As a result, you cannot simply apply the traditional target-based approach without a validated target. The other thing that we do is focus on the chemistry, so trying to match the right small molecule to a newly understood biology. We aim to develop therapeutic breakthroughs, not just a "me too" drug aimed at a target that already exists. I would like to share a quick example. One of our Phase 2 clinical programs focuses on neurofibromatosis Type 1 (NF1), which is a rare tumor predisposition syndrome. Patients develop benign tumors that grow along the nerves and require long-term treatment. Currently, the approved treatments are MEK (mitogen-activated protein kinase kinase) inhibitors, and while that is fantastic for patients to have that option, MEK inhibitors come with significant side effects. For long-term use this can be suboptimal for the patients. As a result, patients, clinicians, and families typically try to avoid taking these drugs until it is necessary as the trade-off between side effects and the clinical benefits for a number of years is difficult to justify.

***"This is what we mean when we think about applying AI to drug discovery. It is really about finding therapeutic breakthroughs, new mechanisms, and first-in-class solutions that will make a difference to patients."***

When we started the program in 2019, and we are now at phase 2 in 2025, we partnered with the Children's Tumor Foundation and what we heard from them was that the NF1 community was looking for a treatment that would be safe for chronic, long-term use and that was not a kinase inhibitor or a traditional cancer drug. Using our AI tools and creative innovative pharmacologists, we set out to find a molecule with a strong safety profile and minimal side effects, and that also had antitumor and anticancer properties. We also aimed for nerve-specific accumulation, because these tumors grow along the nerves. Our phase 1 data demonstrated an excellent safety profile, which is fantastic. Preclinically, we showed that this small molecule accumulates

specifically around the nerve, with a 90-hour half-life around the nerve, compared to a two-hour half-life in the rest of the body. So, it clears rapidly from everywhere else but accumulates in the nerve. It also has very strong anticancer and antitumor properties which reached maximum efficacy in the preclinical models. We would not have achieved this without, first of all, the Children Tumor Foundation and the NF Clinical Trial Consortium, who are incredibly committed and dedicated to finding solutions for patients. We also would not have found this if we had followed the traditional target-based approach. We therefore use AI to look at transcriptomic, phosphoproteomic, and metabolomic data to try and identify first-in-class mechanisms, as well as molecules with a higher affinity for membrane potential, which is important if you want the molecule to reach the nerve. This could potentially lead to a treatment paradigm shift for patients, allowing a potential treatment to be initiated earlier, supporting tumor prevention or secondary tumor prevention, and offering an option that is safe for chronic use. This is what we mean when we think about applying AI to drug discovery. It is about finding therapeutic breakthroughs, new mechanisms, and first-in-class solutions that will make a difference to patients. I want to thank the Children's Tumor Foundation, The NF Clinical Trial Consortium and everyone in the team. It is a very exciting time as we are now in phase 2, and the trial is going well so far.

**Erika Berg (host):**

*Sherri, there has been a lot of discussion about the use of AI to expedite healthcare coverage decisions. One example is in the context of prior authorization. You have looked at both the potential advantages as well as opportunities for harm and abuse. What is your current perspective on the appropriate use of AI by payers, and what are your foremost concerns?*

**Sherri Rose:**

This is an example that is quite dissimilar from what Tim was just talking about as here there is a very primary concern about harms and abuse. We really need humans as a bulwark against error for these algorithms. We have seen class action lawsuits against insurers over algorithms that are designed to restrict post-acute care as well as wrongful denials of prior authorization requests. This has been discussed at the level of congressional committees, for example. A challenge here is that the algorithms currently in use are not performing well. This is true whether the approach uses AI or a checklist for prior authorization. When we think about machine learning and AI systems that rely on these data types and the information being used to make these decisions, often a complex tool will not necessarily be better. Sometimes it is the additional data that is included that might potentially improve predictions. However, this is not always the case. Then, there is the issue of having the same data recorded relatively uniformly for patients, which is typically not the case. So, this question is an AI question, but it is also a transparency question. When we think about patients, how is the decision being made? AI can make that part worse because it is not understood what the basis is for the denial, and a lot of these AI-based denials are being overturned.

**Erika Berg (host):**

*Danton, I was hoping you could speak about AI as an opportunity to deliver greater value for the rare disease community versus the general population. Does AI have some special opportunity in the rare disease community to improve care, compared to more general healthcare concerns?*

> ***"I think that there are a number of qualitative outcomes that communities have been quite excited about, namely, the way social media and AI-driven social media has allowed rare disease communities to connect with each other and find support. I think that those communities have developed strength from that connection, along with a stronger sense of identity and mutual support."***

**Danton Char:**

I do not know if I have any uniquely ethical challenges that would be inherent to that, but I think it will depend on the quality of the data available for a given rare disease community and how well a tool can analyze that data, and what it is able to deliver. I think that there are several qualitative outcomes that communities have been quite excited about, namely, the way social media and AI-driven social media has allowed rare disease communities to connect with each other and find support. I think that those communities have developed strength from that connection, along with a stronger sense of identity and mutual support. I also think that we have all encountered downsides of these social media connections too. There have been some strong instances of misinformation being conveyed within communities, particularly those that were a little more vulnerable from a healthcare perspective. That is something that probably needs to be addressed.

> ***"I believe AI can, on the one hand, empower the rare disease communities, while also empowering the more common disease communities and the general public. In doing so, it can help free up more time within healthcare systems so that nurses and doctors can then focus on the more complex cases, many of which are in the rare disease space."***

**Tim Guilliams:**

From our perspective, because we work very closely with foundations, charities, patients and their families, we think AI can really empower people to start understanding their disease in a different way, potentially receive a faster diagnosis and ultimately bring a sense of agency back to patients, families and foundations. It can also help them begin to use some of the tools to discover new biology and potential molecules that could be used for their disease. Through these partnerships, we see that they come

with suggestions for potential drugs that could work. I think that there is a democratization of innovation for these populations that have been largely ignored for a very long time, and it has the potential to make a huge impact. Another aspect that I believe could be helpful, although I am not a medical doctor myself, but I have a mother who is a doctor, is of the ability to free up expert clinicians from managing the general public and more common diseases. Validated AI tools that are sufficiently reliable can help point people in the right direction, allowing expert clinicians and nurses to focus on the more complex cases. I believe AI can, on the one hand, empower the rare disease communities, while also empowering the more common disease communities and the general public. In doing so, it can help free up more time within healthcare systems so that nurses and doctors can then focus on the more complex cases, many of which are in the rare disease space.

**Erika Berg (host):**

*Danton, you had mentioned earlier that the use of AI in the healthcare setting is still slow to be adopted and that you are seeing a lot on the patient side with patients using AI to explore their conditions. How much enthusiasm or skepticism are you seeing among the broader clinical community (physicians and healthcare providers) around the adoption of AI, both in the clinic and in the patient setting.*

***"A vision of the future is that AI tools could potentially be providing that surveillance function, with your clinicians acting as alert responders. So, when the AI determines an anomaly, a clinician would step in for deeper surveillance."***

**Danton Char:**

I think, like all of society, it is mixed. There are some people who are very enthusiastic about the potential for AI. There are also several areas of strain. There are some visions of changing the way labor functions within healthcare that could be AI-enabled. Right now, your main point of surveillance is your clinician, your bedside nurse or the doctor you see who is assessing you and determining the status of your health. A vision of the future is that AI tools could potentially be providing that surveillance function, with your clinicians acting as alert responders. So, when the AI determines an anomaly, a clinician would step in for deeper surveillance. That gives rise to several potential challenges that we have not yet worked out. I think Sherri alluded to it already. We do not really know that we have any metrics to validate how effective these tools are, or how good those alerts really are. We must look at other high-stake sister industries for comparison. They are not the same, and history does not always repeat itself, but as the saying goes, it often rhymes. We have certainly seen this within the aviation industry, for example, with the Boeing MCAS (Maneuvering Characteristics Augmentation System) question. There has been a big narrative about the challenges Boeing has faced, but one of the challenges that came out of that discussion was whether pilots had adequate expertise to determine when the tool was malfunctioning, to turn it off, and to reassert control over the aircraft. There are all these concerns about deskilling that come up with changing a workflow. It also touches the very nature of labor itself, with questions and concern about how these tools will affect the job, the reasons why people enter the profession, the altruism that motivates them, and the stability of the profession.

**Erika Berg (host):**

*AI models are only as good as the data that is used to construct them, and they require validation. Chunhua, what kinds of data resources are proving most powerful in enabling the type of work you are doing, or other clinical uses of AI, particularly in the domain of rare diseases? Are you seeing increased efforts to establish these data resources specifically for AI applications?*

***"More recently, in the research community, we have also been looking into multimodal AI, which combines genetic data, clinical data, and imaging data to support better diagnosis."***

**Chunhua Weng:**

Yes, I think multiple data types are valuable for developing AI solutions for rare diseases. I mentioned the large-scale EHR data, the medical records data, and particularly the nuanced narrative notes in the EHRs. More recently, in the research community, we have also been looking into multimodal AI, which combines genetic data, clinical data, and imaging data to support better diagnosis. For example, for many rare disease patients, facial pictures and the images of their facial features have proven to be very valuable, when combined with other types of their data, for diagnosis. Dr. Kai Wang and my lab have been collaborating in this space, and our early results show some promise in combining these data for diagnostic purposes. Another important data type is from social media, which Tim and others already mentioned earlier. In the NIH funded Biomedical Data Translator Program a couple of years ago, we saw great success in analyzing posts from rare disease patient community discussion forums. Using this information, they were able to identify potential treatments for some rare disease patients, even before they received a diagnosis, simply by comparing the similarities of their phenotypes and diseases and then reasoning over possible treatment options. Another data source would be the case reports that already exist in PubMed, which is the publicly available literature database for medical research. We have been looking across all of these data types. Recently we also saw an announcement at NIH about plans to create a comprehensive integrated database to support rare disease research. So that is very exciting. As I mentioned, rare disease research often suffers from its small sample sizes. Very often, each institution or organization may only have a limited number of cases. With the maturation of federated learning methodologies, however, I think the trend is moving toward enabling network-wide collaboration.

This allows multiple institutions to leverage federated learning, while keeping their data in their own database and behind their own firewall, yet still being able to share and aggregate evidence to enable collaborative knowledge discovery and treatment discovery for rare diseases. So that is another exciting new trend. Also, within the informatics community, we are still working on addressing data missingness and data bias. Clinical data bias really needs to be based on the better understanding of the healthcare process biases. For example, my collaborator Dr. Wendy Chung shares with me that, very often, data missingness depends on the patients who are sitting in front of you. If the patient is an immigrant and English is not their native language, they may be more reserved, and the doctors or clinicians may be afraid to ask a lot of questions or collect a lot of information. This can influence how much information and how much phenotypic data is collected from different patients. All these issues need to be considered when we think about data quality and data missingness. I live in Manhattan, where data fragmentation is another big issue. Patients move around more frequently than many other places. How do we bring together data scattered across different hospitals and databases to build a complete patient profile? These issues still require a lot of careful work.

**Erika Berg (host):**

*Tim, where are you getting your data from? Is it from similar sources or what is feeding into your algorithms?*

> ***"In rare diseases, the challenge is basically data scarcity, data gaps and, in some cases, the quality of the data. It is therefore incredibly important to map this out. When we start a program, we always start with a data landscape analysis. What is the data available, what is the quality of the data, and what is missing?"***

**Tim Guilliams:**

I would first like to echo what Chunhua just shared. In rare diseases, the challenge is basically data scarcity, data gaps and, in some cases, the quality of the data. It is therefore incredibly important to map this out. When we start a program, we always start with a data landscape analysis. What is the data available, what is the quality of the data, and what is missing? Then I go back to the team and to the foundations and say, "If you had a magic wand, what data would you generate?" There is always a long wish list, and we must make trade-offs and choose the areas that will give us the greatest insights as we are here to find novel rare disease mechanisms and then small molecules that can act on those mechanisms. Because we do not live in a very data-rich world, we need to make the most of what there is and avoid approaching the problem with blinders on, for example, assuming that because everyone else working on NF1 is developing a kinase inhibitor, we need to do more of the same. Instead, once we have this data landscape and analysis completed, we can try and analyze all of it and see if any of it can provide new insights or reveal something novel. Then, we try to observe patterns across data types. For NF1, for example, this is how we arrived at our breakthrough. We also make a deliberate effort to learn from places where there is more data, namely the common diseases. We use algorithms to try and derive insights from common diseases and see how this can help us fill in data gaps from rare diseases where we are missing data and cannot generate it. The challenge here is a bit different than within the common disease space. From a biological perspective, the richest sources of insight come from your single cell transcriptomic and proteomic data, so those very rich biological data sets, ideally from patient derived samples or cell lines, which are hard to obtain. This is where clinicians and foundations can play a critical role in helping to generate, collect, and share these data, and it is often where we see the biggest breakthroughs. All the other data types that Chunhua mentioned are also extremely useful. The real-world evidence, the phenotypic data, and there are a number of other data types.

In today's world, the algorithm itself and the analysis are less of a bottleneck. There are still things that need to be done correctly, and challenges remain, but the bigger issue is the quality of data that you can generate, rely on, and then analyze in an objective way with less bias. I think that there is some real progress happening in that space, particularly as we approach it in a multimodal way, where you can have scans, genetic data, transcriptomic data, and real-world evidence and analyze this across, what we call, the "lasagna" data stack of layers. Then whatever gives us an insight, or a breakthrough is a win. Whether it is generated by an LLM or another type of model, it does not really matter to the patients.

**Erika Berg (host):**

*Sherri, there are many applications of data that are predicated on the analysis and interpretation of real-world medical data and other personal information. What are some of the practical concerns with respect to patient protection and privacy, and other similar issues?*

> ***"We already know that for the general population it takes maybe three pieces of data, or sometimes even fewer, from an EHR for a person to be completely identifiable. With rare disease patients, it could be a single binary flag for their health condition combined with a piece of their zip code, and then the rest of their data is identifiable. So, there are many questions around patient protection and privacy that have not yet been answered, and I think this is particularly problematic for the rare disease community."***

**Sherri Rose:**

I will dovetail on some of the comments from Chunhua and Tim. The data is paramount, and AI and machine learning is secondary to the data. When we think about what it means for patient protection and privacy, there are several concerns we could think about. One of the topics that I know Danton has worked on is whether patients are going to be notified that an AI tool is being

used? For example, some large medical centers are using AI-based transcription and are not telling patients that the visits are being recorded. They have decided that it is not required. When I sign onto Zoom and am being recorded, it notifies me and I have to click that I agree. Yet, if I am going to a clinician's office and that information is being recorded, a decision has been made in certain centers that the patient does not need to know. This raises further questions about where that data is stored and for how long. A lot of the time there are assurances that it is stored locally and then deleted. However, as we have seen with data breach after data breach, what does being deleted mean, especially for individuals in the rare disease community? We already know that for the general population it takes maybe three pieces of data, or sometimes even fewer, from an EHR for a person to be completely identifiable. With rare disease patients, it could be a single binary flag for their health condition combined with a piece of their zip code, and then the rest of their data is identifiable. So, there are many questions around patient protection and privacy that have not yet been answered, and I think this is particularly problematic for the rare disease community.

**Erika Berg (host):**

*Danton, do you want to talk about the example that Sherri mentioned?*

**Danton Char:**

I think this is germane to all of us. The question of what patients want to know, and need to know, about AI being implemented into their care, and whether considering AI separately is a form of AI exceptionalism. There are many things we do in healthcare and decisions we make, such as the supplies we use or the drug vendors we purchase from, that patients are not informed about, even though these choices can have a significant impact on their care. With AI, we have talked about trying to develop guiding metrics for our own institution. We are using something now, but we are watching it closely and are willing to revise it if we view it differently. If we feel that the risk of harm is high from an AI tool being involved in someone's care and/or a patient could meaningfully opt out, then we feel that informing patients makes sense. If it is very much a background AI that does not have much of a footprint and that they could not meaningfully opt out of, such as the use of AI tools for prior authorization, claims, and submissions, we do not tend to talk to patients about it. That has been consistent and driven by our patient partner panel. We work with a group of patients who are learning alongside us about AI tools and are actively engaging with these discussions. They felt that this is a reasonable first step, because there is clearly data that shows the harms of opening a fire hose of information on a patient, particularly when they are under duress. Over-disclosure can lead to panic, anxiety about small decisions, and loss of focus on the critical decisions that their minds need to be focusing on. We are trying to strike a delicate balance. I do not pretend that we have gotten it perfectly yet, but this is our initial guidance.

**Erika Berg (host):**

*Sherri, where are we in clinical settings with respect to establishing standards and guidelines for the ethical and transparent use of patient data? The use of AI in these clinical settings sounds a bit like a patchwork, with variations from institution to institution, but are there standards?*

> ***"We have some newer or updated guidelines like TRIPOD+AI for prediction algorithms, but I would say that we are very far from the consistent use of these types of standards and guidelines. This needs to be something that the community agrees that we must be doing."***

**Sherri Rose:**

I will reiterate some of the things that Danton was highlighting. Yes, there are institutional processes to decide when and if they would deploy machine learning and AI tools. There is the institutional governance, and sometimes there are also state and federal policies. However, when we think about the general development of machine-learning and AI algorithms, there are some standards and guidelines for researchers, but they are not widely adopted or used, and that is a significant problem. Sometimes they are adopted and enforced when they are required by either medical journals or funders. But it is definitely a patchwork. We have some newer or updated guidelines like TRIPOD+AI for prediction algorithms, but I would say that we are very far from the consistent use of these types of standards and guidelines. This needs to be something that the community agrees that we must be doing. However, that usually involves an enforcement mechanism, otherwise it does not happen.

**Erika Berg (host):**

*We have heard a lot about AI hallucinations, or errors by AI. How reliable is it? Have you in your research experienced these sorts of hallucinations and how should the medical community think about these issues with respect to patient safety?*

**Chunhua Weng:**

I think that to address the hallucination problem we can develop knowledge graphs and knowledge bases and then combine them with large language models. The technique we have been using is retrieval-augmented generation. In this way we can always anchor the information to the facts and to the rules in the knowledge base. We also studied some algorithm topics such as the lost-in-the-middle phenomenon. That is another phenomenon when large language models are used to rank the retrieved documents. We can develop more algorithms to potentially detect these issues and then mitigate the risk. I remain optimistic about these issues. Technical issues are relatively easier to solve and whenever

we discover one we can always explore and seek new solutions to address it by leveraging the knowledge out there, including the rich knowledge in the literature, and combining it with large language models. I think the more challenging issues are really the social, ethical, legal and policy ones that have been mentioned by Sherri and Danton. Those are the bigger challenges right now.

**Erika Berg (host):**
*Looking forward, are there domains of medical care where you think AI could have particularly powerful benefits in the future? And do you see any red lines in terms of where it should not be used?*

> ***"Looking five to ten years from now, I see the potential for breakthroughs, not just incremental improvements, through foundational models applied to multi-omic biological data that help us understand the language of life."***

**Tim Guilliams:**
I think that if we project five or ten years ahead, what may potentially become possible is the use of foundational models that have now been trained on natural language, so English, where we have seen incredible improvements in performance and understanding. I believe one of the biggest opportunities now is to create and train foundational models that can understand biological data and chemistry, in other words, models that are biologically aware and chemistry aware. They would not help us understand the natural language of English, but rather the language of life, which is your biology. Of course, it is too early to see any meaningful impacts from this approach because a few years ago it did not even exist. That is why I believe this could potentially lead to the biggest breakthroughs in human disease understanding, in a way that we cannot comprehend ourselves. The red lines would be following the regulations and ensuring patient safety to make sure that any promising breakthroughs are agreed upon with the FDA and included in the IND packages for clinical trials. This is the balance needed to maintain patient safety. Looking five to ten years from now, I see the potential for breakthroughs, not just incremental improvements, through foundational models applied to multi-omic biological data that help us understand the language of life.

**Danton Char:**
I agree with Tim. I think there is a lot of optimism in what AI tools can do. I do still have reservations about the economics of making them do what they do and about translating that vision into the amount of data and funding required, and specifically whether the healthcare system will be able to afford it. From a clinical standpoint, I think the things that have the most meaningful impact on clinician-patient interactions are those that move the many current distractions that get between you and your healthcare provider into the background. AI tools that could potentially shift billing and charging tasks away from the direct clinical encounter could be very beneficial in allowing clinicians to focus more on care. What we are seeing, at least anecdotally, is that when AI tries to replace the clinical interaction itself, there is resistance. Few patients would want an automated phone tree delivering their healthcare.

**Chunhua Weng:**
I think that keeping humans in the loop will still be very important. We often see people on the news worrying that AI will eventually replace or destroy humans. These are scary narratives, but from my perspective, I feel that AI in healthcare has great potential and can empower patients, particularly through education, as it provides them with more information. I am also optimistic that AI can handle some simple tasks so that the more complex cases can be saved for the experts. That could be another positive change that I am looking forward to.

**Sherri Rose:**
I will bring a few threads together. I think it is important to carefully consider the data type, as far as the domains that could be particularly powerful in other areas, for example imaging data. These tools are often just not as well suited to categorical or integer data types. Oftentimes these are the types of data that are used in a lot of population health research. I also want to echo what Chunhua and Tim have said: seeing reproducible and generalizable results is going to take years. This is what we saw previously with earlier machine learning algorithms, and I agree with that. I want to reiterate that the default should not be an algorithm that will solve every problem. It is often the case that it will be a much more challenging solution, especially when we are thinking about issues of access to care and social drivers of health. Simply making a small change to an algorithm, or introducing an algorithm, is not going to solve that problem. When I think about red lines, they would be poorly considered algorithms, of which there are currently many, developed in a rush to publish or to bring products from the tech world to healthcare. That should definitely be a red line.

## The ethics of rare disease: Balancing the needs of the few with the needs of the many

**The ethical challenges surrounding rare diseases lie at the intersection of compassion, innovation, and equity. How should healthcare systems, policymakers, and society balance the urgent needs of individuals living with rare conditions against the broader priorities of public health? This discussion brings together experts in policy, health economics, and ethics to examine how moral and practical considerations shape decisions about research, regulation, and resource allocation. The panel will explore the growing role of patient-led evidence and advocacy in shaping fairer systems of care, the global economic frameworks that inform reimbursement and access to rare disease treatments, and the ethical dimensions of genomic testing, fairness, and family experience.**

**Together, these perspectives illuminate how societies can pursue both equity and efficiency in addressing rare diseases—ensuring that progress for the few ultimately benefits the many.**

**By the end of this webinar, participants will:**

- **Understand the ethical and economic frameworks that guide decisions about funding, access, and reimbursement for rare disease treatments.**
- **Explore how patient advocacy, data generation, and policy reforms are influencing the ethics and practice of rare disease research and care.**
- **Identify strategies for balancing fairness, innovation, and sustainability in healthcare systems that serve both rare and common diseases.**

## Panelists

**Annie Kennedy**
**EveryLife Foundation for Rare Diseases, Washington, DC**

**Ulf Persson, Ph.D.**
**Swedish Institute for Health Economics (IHE), Lund, Sweden**

**Hadley Stevens Smith M.D.**
**Harvard Medical School, Massachusetts, USA**

**Mark Trusheim, M.S.**
**Tufts Medical Center, Massachusetts, USA**

**Erika Gebel Berg, Ph.D.**
**Science/AAAS, Washington, DC; moderator**

## The Conversation

**Erica Berg (host):**
*The ethical challenges surrounding rare diseases sit at the crossroads of compassion, innovation, and equity. How do we, as healthcare systems, policymakers, and as a society, balance the urgent needs of individuals living with rare conditions against the broader priorities of public health? Today, with a brilliant panel, we will explore the growing impact of patient-led evidence and advocacy in shaping fair systems of care. We will look at how global economic frameworks influence reimbursement and access to rare disease treatments. We will also consider the ethical questions tied to genomic testing, fairness and the family experience. Ultimately, our goal is to shed light on how societies can strive for both equity and efficiency in addressing rare diseases so that progress for the few can ultimately benefit the many. I would now like to take the opportunity to welcome our excellent panel. I will give each of them a chance to say hello and introduce themselves.*

**Annie Kennedy:**
My name is Annie Kennedy. I am the Chief of Policy, Advocacy and Patient Engagement for the EveryLife Foundation for Rare Diseases. We are an evidence-based policy and advocacy organization that represents our broad rare disease community here in the U.S.

**Hadley Stevens Smith:**
I am an Assistant Professor of population medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute. I am also a faculty member of the Harvard Medical School Center for Bioethics. My research program evaluates the clinical, patient-centered and economic impacts of genomic medicine interventions. Much of my research has focused on evaluating the use of genomic sequencing to screen for and to diagnose rare conditions for newborn and pediatric patient populations. I have been particularly interested in advancing the methods that are used to capture the impact of genomic sequencing and rare disease diagnoses for children and their families.

**Mark Trusheim:**
I am the Strategic Director of NEWDIGS at Tufts Medical Center, where since 2010 we have been running multi-stakeholder consortiums addressing the challenges of rare disease. Back then, we began with the regulatory challenges of how to deal with very small populations compared to the classic large population drugs and conditions. Then in 2017, we shifted to include the downstream market access needs for payment and reimbursement, particularly for cell and gene therapies, but also for the range of rare disease therapies. So, we have been at this for about 15 years or more.



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**Ulf Persson:**
I am a health economist and nowadays I am a senior advisor at the Swedish Institute for Health Economics. I have also been involved in building the Swedish Reimbursement Authority for Pharmaceuticals. As a member of the board, I had a lot of experience with the challenges of getting new orphan drugs into the reimbursement scheme.

**Erica Berg (host):**
*Mark, how high would you say are the structural barriers for medical innovation in the rare disease space compared to more common medical conditions, such as cancer, and to what extent have you seen this barrier be lowered in recent years, if you have indeed seen that?*

**Mark Trusheim:**
I think rare diseases have experienced a striking paradox over the past decade or so. If you look at rare disease writ large, the barriers have been coming down. There has been an explosion of rare disease therapies approved over the last 10 or 15 years and there has been more research in that space. However, if you compare it to the need in the rare disease space, and if you are involved in any way in an individual rare disease, the barriers remain astonishingly high, both in terms of securing research funding and finding patients to help understand the mechanisms and natural history of these conditions. There is still a tremendous amount of work to be done compared to the larger conditions that have entire institutes at the NIH dedicated to them. It is very different for any individual rare disease to move forward. So, it is a tremendous paradox: on one hand, a great success; on the other, we still have thousands of diseases that receive no attention at all. If you suffer from one of those, you feel like you are starting from nothing, which in many cases, unfortunately, is rather true. The barriers are simultaneously extraordinarily high and, in some ways, far lower. We are seeing this now as an established approach and field in drug development, whereas 15 years ago that was not the case.

***"One of the key concerns in the rare disease space is that most rare diseases remain hidden because we do not have a reliable way to see them in our datasets in our health systems."***

**Annie Kennedy:**
I think Mark set that up really beautifully. Maybe I can just fill in with some statistics and context around why that is. Today, rare diseases affect approximately 30 million Americans in the U.S., and we understand that more than 50% of people diagnosed with rare diseases are of pediatric age when they are first diagnosed. We also know that the majority of those diseases are fairly rapidly progressing and that right now fewer than 5% of rare diseases have FDA-approved therapies. So, there is a significant unmet need and urgency. That really speaks to what Mark was saying, in that we still have a high threshold for need in the rare disease space. But perhaps we should talk about what those thresholds for entry into rare disease might be. Because I think we are going to dig into that and how those incentives have been established over time.

By nature of the definition, rare diseases have very small patient populations. Even in some of the more common rare diseases, as we learn more about those conditions, we learn about mutation specificity. So, we are learning about subpopulations within those populations. This adds to the complexity of designing clinical trials and studying those patient populations. In our rare communities, we have nascent natural history, and we are learning so much about the importance of having longitudinal data around our communities. We have significant diagnostic delays in rare disease. At the EveryLife Foundation we conducted a study about this, and we found that the mean diagnostic odyssey for rare disease patients is close to six years. That is a very conservative estimate. That means that from the time a parent or an individual first identified that there was a concern, it took over six years to get a diagnosis. We also know that this includes seeing 17 providers and making multiple out-of-state trips, which requires a coverage and reimbursement system that allows for that travel, and the ability for someone to afford that. We will explore those costs throughout this conversation.

We also have data that shows that it takes 15 years and over $2 billion to develop a therapy, and that most therapeutic concepts will never make it into the regulatory environment. Finally, once there is an FDA approval, there is a very complex access ecosystem that makes reimbursements for many of those therapies extremely difficult. So, those are all the complexities.

One of the key concerns in the rare disease space is that most rare diseases remain hidden because we do not have a reliable way to see them in our datasets in our health systems. We often use ICD codes, or the International Classification of Diseases, to identify rare diseases. While we estimate that there are more than 10,000 rare diseases, we have fewer than 1,000 ICD codes for rare diseases. As a result, even once a diagnosis is made, we are unable to track it, see it, identify it, or study it in a systematic way in our communities and across our health systems. There are so many hurdles and barriers, and while we are working hard to overcome them, we still have some massive challenges to face. That said, I am really grateful that we can have this conversation today to talk about what we have done to overcome many of those hurdles, and to even reach a point where we have approved therapies for 5% of rare diseases, and patients alive today, who ten, five, or even three years ago, would not have been.

**Erica Berg (host):**
*Ulf, I am wondering, from your perspective, if you are seeing the same progress and the same lowering of barriers, and whether you are seeing anything different in the European ecosystem?*

***"In some countries, like in the United Kingdom and in Sweden, we understand that we need to pay a little more for orphan drugs than for other treatments. That can be linked to the high degree of disease severity in these patient populations. We are searching for different justifications for a separate approach to orphan drugs. This is an ongoing process aimed at gradually reducing these barriers."***

**Ulf Persson:**
I think if we take it from the payer's point of view, we have an increased awareness that this is a big problem because it has to do with the number of patients. It is very expensive to develop a new drug or compound. To give an example, it costs about the same amount to develop a new drug as it does to build a big bridge between Sweden and Denmark, a bridge that is 10 miles long. That cost must be spread across the consumers, payers, and the patients. If we have a drug for a more common disease, the cost can be spread across many patients, with payers covering it. When we have orphan conditions and orphan drugs, we only have payments from a few patients. So, this is one of the explanations why the prices used to go up. We are talking about the prices for orphan drugs which have been considered to be a very big problem. Many times, payers are not used these higher prices. They are used to very low prices per patient, and we have traditionally talked about the number of patients treated, and so on. But now we have a situation where we can identify the patients who are most likely to respond to a treatment. That means we are treating a very small number of patients. What I have seen during the last few years, particularly from Sweden and some other European countries, is that there is growing awareness that we need to find ways to ensure a faster uptake of these drugs, rather than waiting until the patents expire or anything like that. So, there is a strong understanding that we need to develop new approaches. In some countries, like in the United Kingdom and in Sweden, we understand that we need to pay a little more for orphan drugs than for other treatments. That can be linked to the high degree of disease severity in these patient populations. We are searching for different justifications for having a separate approach to orphan drugs. I think this is an ongoing process and I can see that this is a process where we are trying to reduce the barriers more. So I am optimistic about this.

**Erica Berg (host):**
*Annie, to what extent has the burden of maintaining sustained focus on rare diseases fallen on the individuals themselves and their families?*

***"Before we even had federal investments into those research pipelines and could have handoffs with industry in those spaces, it was patient groups that were doing the work of funding registries and natural history studies."***

**Annie Kennedy:**
I like to use the saying, "It takes a crowd to draw a crowd." In the rare disease community, garnering interest in rare diseases often falls to the rare disease parents and individuals living with rare diseases. They frequently shoulder the responsibility of spurring that initial investment and interest for individual rare diseases. What we have seen is patient communities galvanize, come together, build those animal models, and drive scientific investment. Many times, we have patient communities who have been the first ones to fund the scientific communities and invest in the academic researchers who have developed the clinical trial endpoints and mechanisms and biomarkers. Before we even had federal investments into those research pipelines and could have handoffs with industry in those spaces, it was patient groups that were doing the work of funding registries and natural history studies. We have also seen patient groups de-risk participation in rare disease development, not just on a disease-by-disease basis, but collectively, by looking at where guidance is needed to better understand therapeutic development in rare diseases and where we need new regulatory pathways and new incentives for therapeutic development. We have had creative legislation and statutes, as well incentives like the Rare Pediatric Disease Priority Review Vouchers and the Orphan Drug Act. That work has, once again, been led by the patient community, to create an ecosystem that de-risks participation for investors and developers to work within our spaces, while enabling individual rare disease communities to function effectively and move products forward.

**Erica Berg (host):**
*I think we have set the stage appropriately and I wanted to move on now to start talking about neonatal sequencing. Hadley, how has the rapid evolution and the falling cost of genome sequencing benefited the rare disease community, enabling earlier and more definitive diagnoses and potentially setting them up for interventions?*

**Hadley Stevens Smith:**
One of the major ways that the falling cost of genome sequencing has benefited the rare disease community is through the clinical translation of this technology and through the basic science advances that have gone hand in hand with that. So, by that, I mean moving this technology from bench to bedside, so that genomic sequencing is now broadly available as a diagnostic tool in clinical care. That increasing availability in clinical care has allowed us to better understand the impacts in both the clinical realm, what we refer to as clinical utility, and on patients and their families, which we call personal or perceived utility. From a basic science perspective, those advances in understanding the relationship between genetic variants and clinical presentation have enabled scientists and doctors to make more precise diagnoses for a greater number of rare conditions. This growing evidence base, and understanding both clinical and personal utility, is very important for increasing evidence that is useful for healthcare payers, as they make coverage decisions about which tests to cover and for which patient populations. In turn, this helps make genomic sequencing gradually, and still imperfectly, more broadly available.

One setting where we know that genomic sequencing can be

particularly useful in terms of establishing diagnoses and guiding care is in the neonatal intensive care unit. Genome sequencing performed early in the diagnostic pathway (i.e. the beginning of the diagnostic odyssey), for the most critically ill infants, and especially with a rapid turnaround time of less than a week, provides diagnoses for about 30% to 50% of the critically ill infants who are tested. Moreover, it impacts care decisions within a given hospital admission for about 20-30% of those tested infants. Genome sequencing can also lead to substantial cost savings to healthcare systems by informing those care decisions and by reducing inpatient length of stay. When compared with a gene panel test, which is less comprehensive, one recent analysis found that rapid genome sequencing early in the hospitalization resulted in cost savings of more than $150,000 per patient over one year from the healthcare sector perspective. Obviously, realizing these benefits, both for child population health and in terms of cost savings to the health system, requires that rapid genome sequencing be both accessible and taken up by patients and clinicians.

**Erica Berg (host):**

*Do you have a sense of how broadly accessible neonatal genetic testing is? I know you were saying specifically in the intensive care ward, but is it accessible more generally, such as for the curious or anxious parent? What is the status of that?*

> ***"Genome sequencing is a newer technology that has been more recently introduced into clinical care, but for the past 10 years or so, exome sequencing has been available as a diagnostic test and payers are increasingly covering this test."***

**Hadley Stevens Smith:**

There are several settings in which we can consider the use of the same or very similar technologies. Here I would lay out three different use cases. One is for diagnostic testing, such as that performed in neonatal intensive care units or in genetic outpatient clinic settings. This type of testing would typically be used to diagnose a patient with a suspected genetic condition, in other words, those whose clinical presentation warranted genetic testing. A second setting where we are seeing a rapid rise in the use of genome sequencing is in screening. As a complement to traditional newborn screening, genomic sequencing approaches are now being used to augment that neonatal screening and to expand the range of conditions that can be screened for early in life. Then, a third use case would be direct to consumer testing. We are also seeing significant growth in this market, particularly for early childhood testing aimed at understanding disease risks and, in some cases, traits. Overall, in the diagnostic setting, both exome and genome sequencing are now much more widely available in clinical care than they were five or 10 years ago.

Genome sequencing is a newer technology that has been more recently introduced into clinical care, but for the past 10 years or so, exome sequencing has been available as a diagnostic test and payers are increasingly covering this test. That is a very critical piece of the access puzzle. This is true on both the commercial side and the public payer side. For example, there are now 18 states that have covered rapid genome sequencing under Medicaid, and legislation that would provide that coverage has been introduced in an additional nine states. This is an area with significant advocacy activity and growing recognition at the legislative level that this type of testing can provide important benefits both for families and healthcare systems.

> ***"We continue to have a real barrier, not just with the uptake of rapid whole genome sequencing, but also with the uptake of newborn screening and other diagnostic testing across rare disease in general, is that providers, especially pediatric providers, are trained to look away from suspecting rare diseases when they are considering a diagnosis."***

**Annie Kennedy:**

Can I build on what Hadley was talking about? Because I think it gets to your question. One of the main barriers to this testing is providers ordering these tests. Where we have seen a lot of success is within the pilots, where rapid genome sequencing has been piloted within the NICU setting and acute hospital settings. That is where we have had so many wonderful learnings and those experiences have driven so much of the momentum behind the advocacy work, such as our ability to advocate for coverage within the state Medicaid programs. Where we continue to have a real barrier, not just with the uptake of rapid whole genome sequencing, but also with the uptake of newborn screening and other diagnostic testing across rare disease in general, is that providers, especially pediatric providers, are trained to look away from suspecting rare diseases when they are considering a diagnosis. In fact, if you know anything about rare diseases, you have probably seen the zebra logo. The zebra is the logo for rare disease, not just because it is cute and catchy, but because providers are often taught that if you hear hooves, look for horses, not zebras, when thinking about rare disease and about diagnostics. Rare diseases are individually rare. That is why they are called rare diseases, but collectively they are not. I mentioned earlier that there are more than 10,000 rare diseases. That number increases every day. It is estimated that more than 10% of the U.S. population is living with a rare disease. Many people have multiple rare diseases. So, we need to change that paradigm so that providers are not looking away from a rare disease, but are adding it to their diagnostic toolbox. There are incredible efforts underway, funded by both public and private entities, that are looking at how we can introduce triggers into our data sets and learnings, so that when providers see multiple visits to an ER that are out of the norm, they can short-circuit that diagnostic odyssey. This is incredibly important. We need to do better because, as Hadley said, we have the tools and the technology, but we need to be using them. Because it does not only get somebody to appropriate care and treatment, but it also often unlocks someone's eligibility for benefits, health coverage, appropriate accommodations in schools and in workplaces, and very importantly, it enables the individual to have a community. We talk about N of 1 or N of few, but if

we are identifying and diagnosing diseases effectively, we may discover that there are actually N of 2 or N of 3. We may find communities simply because we are diagnosing conditions more often. So, this is really a big plug for provider education and for shifting the paradigm around rare disease.

**Mark Trusheim:**
I am a health economist, like Ulf. Part of this is the cost of whole genome sequencing falling. If we did it for everyone, it would fall by another order of magnitude, which then makes the whole cost benefit analysis better for every patient. I know from a drug developer standpoint, that finding patients is very hard because they are so rare. So, having that kind of national screening and understanding is important. It also helps us from an equity standpoint, so that access to rare disease care is not limited to "billionaire babies", which is a challenge. If you are wealthy enough, you can pay for the extra genetic testing out of pocket, if it is not covered. However, if you are not, then you are often overlooked and sent on these 6- or 15-year diagnostic odysseys, if your condition allows you to live that long through the whole process. So, I think this shift, from a diagnosis-driven approach where a clinician must have a hypothesis ("I think it might be a zebra, therefore maybe I will order the test") to an approach where this is more standard like running a complete blood count, is important. They do not have a hypothesis that I have some blood issue. It is just a standard test that is run nearly every time you check into an ER. Having this done once for patients, to know what their genetic abnormalities are, seems like a fantastic tool to understand what is ahead. It may not show up in the first three months, but it will show up in the first year or it may not be until you are six or eight that you will start seeing symptoms. To be able to get out ahead of this is increasingly cost-effective and inexpensive and yet we do not provide the access to it. It could transform the whole ecosystem. It is basic and straightforward, and it would be fantastic to have this required as a standard part of care. Parents may opt out, of course, but it would be great if it could become part of the standard care package.

**Erica Berg (host):**
*Ulf, what is the status of access to neonatal testing in Sweden and in Europe, and how are the economics playing out, particularly the balance between the cost of testing larger populations and the potential for long-term savings associated with earlier diagnosis?*

***"This means that we have a lot of opportunities, but also a lot of uncertainty. As a result, those who are responsible for paying for these treatments and deciding whether to introduce them into healthcare systems must make the best possible judgment they can about the value of a treatment over very long period of time."***

**Ulf Persson:**
Yes, this also has to do with identifying patients in the same way here. One very important point is that we now can use these new gene and cell therapies that can almost cure patients or at least have the potential to do so. The problem with them is that they often involve a short treatment period followed by a long period of benefit. In some cases, it may be a one-time or single treatment that will last for many years and can more or less cure the patient. We do not know whether the effects of these treatments will wane over time or how long they will last until they start to be less effective. This means that we have a lot of opportunities, but also a lot of uncertainty. As a result, those who are responsible for paying for these treatments and deciding whether to introduce them into healthcare systems must make the best possible judgment they can about the value of a treatment over very long period. This also means that the payment should be linked to the treatment differently. We traditionally pay for the treatment, not for the benefit later. These treatments justify a very high payment because they are so effective in many cases. But we do not really know the long-term outcomes. So, we have a lot of uncertainty. This can put a lot of pressure on the healthcare budgets because they can go up to $2 million per treatment per patient, and that can be very difficult. So, we are really searching for different ways of justifying a high price and ensuring access to these therapies and getting them into the budgetary system as smoothly as possible. This is another big challenge for the payer.

**Erica Berg (host):**
*Let us now talk about investing in rare disease treatments. Mark, can you share with us what some of the distinct challenges are when thinking about return on investment for both diagnostic and drug development programs in the domain of rare diseases where again, the patient populations are small, but the potential of these treatments to cure these diseases is tremendous.*

***"Some of the gene therapies cost up to a couple of million dollars, but many of them are expensive cancer therapies, costing several hundred thousand dollars a year, which is in line with what cancer treatments cost. We do not bat an eye at spending that amount on cancer, but for a rare disease, suddenly it is a problem."***

**Mark Trusheim:**
Return on investment has two components: how much you invest as part of the game and how much you make or the revenue that comes in. Rare diseases suffer on both sides of this. The investment required to create an effective therapy for a rare disease may not be substantially lower than the investment required for a large population, such as obesity, where GLP-1s are the current hot topic. Finding ways to make the cost of developing a therapy for a small population cheaper and faster is important. We are seeing breakthroughs across the board: from regulatory improve-

ments that speed up the process, such as requiring fewer trials or accepting endpoints that are easier to measure, to AI and gene editing techniques to help improve our success rates in finding what the right therapy is before it enters clinical trials. We have great hope there. The other challenge, which Ulf has pointed out, is once you have been approved, how much can we afford to pay for these therapies? Compared to other drugs, they can be unbelievably expensive, which seems unfair. Some of the gene therapies cost up to a couple of million dollars, but many of them are expensive cancer therapies, costing several hundred thousand dollars a year, which is in line with what cancer treatments cost. We do not bat an eye at spending that amount on cancer, but for a rare disease, suddenly, it is a problem. There are also other areas, where we do the same sort of thing, but it is not medication cost, so we do not bat an eye at funding either. We talked about neonate units. It is not unusual to incur multimillion-dollar neonatal costs, but that comes out of a medical budget, not out of a drug budget, for these payers. So, we are used to paying multiple millions to get an infant off to a good start, but paying multiple millions to give them a therapy to get them off to a good start is somehow offensive and difficult. We have children and adults with traumatic injuries. Again, the cost of treating a traumatic injury is around 3, 4, or 5 million dollars. The total cost of that type of care is not an unusual charge if you talk to the insurance companies. However, spending that amount to help a sickle cell patient not have to go to the hospital ever again is seemingly out of bounds. So, the challenge on the revenue side is that we do not compare the cost of these drugs to other life transformative therapies and treatments that just happen to fall on the medical side instead of the drug cost side. That leads to false comparisons. Another aspect that we sometimes overlook is that these therapies tend to be reasonably effective on every individual. In contrast, other therapies that we pay more money for overall, such as Type 2 diabetes therapies or statins for heart disease, you have to treat 40, 50, or 100 patients to avoid one death in those spaces. When you take the total cost of the drug, it may be lower per patient, but the overall expenditure per life saved or improved may still add up to multiple hundreds of thousands of dollars. Rare disease therapies are in a sense cursed by being effective. They help a few patients and do tremendous things, and yet because they did not have to treat 400 patients to get one to do well, like you have to do with some of these other therapies, they are somehow viewed as too expensive.

We must rethink return on investment when we consider how these treatments are paid for, and we must be able to develop these drugs faster, quicker and at a lower cost. Because if the investment were only a few million dollars instead of hundreds of millions of dollars, you would not need to make a billion dollars back just to cover the multiple hundreds of millions you spent on its development. For example, if it only costs $10 million and you make $50 million back, that is a huge return and something financial people would be very excited about. So, those are the two angles to consider

**Ulf Persson:**
I agree with Mark. I think that sometimes we have to budget in the benefits side as well. For example, if we give a treatment to a patient with hemophilia, as there are many gene therapies being developed for hemophilia, there is a significant drug cost saved from factor VIII treatment over a patient's lifetime. Factor VIII prophylaxis is a very big burden for the payers and if we can reduce that cost with a one-time treatment that eliminates the need for these factor VIII treatments in the future, we can free up a big budget to pay for the immediate gene therapy costs. The problem is that many times we do not have this money available. So, we need to find some clever ways to secure the budget immediately upfront, even if we understand that there will be huge cost offsets later on in the patient's lifetime. Sometimes there is a budget available, but it is not linked to the healthcare provider in the same way. For example, we have a lot of situations for severe conditions in children where the progression of the disease means that they will require municipally funded services or home services. That is a completely different budget. But that is a budget that can be reduced if we can treat them successfully at a young age. We need to have a link between different kinds of budgets as the disconnection is another problem that we have seen so many times.

***"What we have seen is that there is so much wasteful spending. When we talk about a six year diagnostic odyssey for something that could be diagnosed in the first 24 hours of life, we are talking about wasteful spending of close to a million dollars, or potentially more if we are talking about an extended ICU stay."***

**Annie Kennedy:**
First of all, this is a sweet spot for us. As a patient community, we have done a lot of work to move from those back of the envelope calculations around what it means to live with a rare disease, to actually collecting data around the lived experience of rare diseases. We have collected data to show that in one year, the economic impact of rare disease was close to a trillion dollars. That was in 2019, and the lion's share of those costs (close to 60%) were not costs that were being absorbed by the healthcare system. They were costs that were being absorbed directly by families and the community. This really underscores both Ulf's and Mark's points that there are costs showing up elsewhere that are still prescribed but are being paid for out of pocket by families or by other elements of the healthcare system. This means that we are not comparing apples to apples when we are having these conversations.

***"Investments in rare disease are strategic investments in our healthcare system, but we do not think about it that way. We must struggle and fight for funds in the rare disease space and incentivize people to work in our spaces."***

The other thing is when we have these conversations around investing in therapies and diagnostics, the goal is not to cut the cost per person, it is to make strategic investments to optimize outcomes within the key therapeutic window and to eliminate waste. What we have seen is that there is so much wasteful spending.

When we talk about a six-year diagnostic odyssey for something that could be diagnosed in the first 24 hours of life, we are talking about wasteful spending of close to a million dollars, or potentially more if we are talking about an extended ICU stay. I think those are the conversations we need to be having and then doing something about them. Those are policy shifts for us. The other thing is, this really comes down to a paradigm shift, and underscores something that Ulf was just saying. We need a paradigm shift around what we are willing to invest in rare disease. Mark just made some wonderful analogies about what we spend and what we are willing to risk and tolerate in other disease areas. However, we are not willing to make that same investment in rare disease research. I pulled some numbers, and when we look at what we have been spending federally in rare disease, in the U.S., we are talking about amounts that can be counted in the millions. In contrast, federal cancer funding was around $8 billion at the NIH alone, with an estimated $57 billion investment in R&D. Now, we should absolutely be investing that. About one in five Americans is estimated to live with cancer, but there is also about one in 10 with a rare disease. Should we have such a wide disparity between what we are investing in rare diseases and what we are investing in cancer? Probably not. And we are not having the same discussions when talking about what we are going to invest in a patient with a cancer therapy compared to a patient with a rare disease. We really need to be thinking about this differently.

The other thing is that when we invest in rare disease therapies, what we learn from those investments can be immediately extrapolated to more common diseases. To give an example, bisphosphonates were first studied in rare bone diseases, and they are now being used for osteoporosis more broadly in the community. When we are learning about how to treat cystic fibrosis, we are now applying those learnings to other genetic diseases. The same is true for sickle cell disease. Advances there are being applied to other rare diseases. These investments in rare disease have a much broader impact. PCSK9 inhibitors (Proprotein Convertase Subtilisin/Kexin type 9), for example, were studied in a rare genetic form of hypercholesterolemia. This is now how we treat cholesterol broadly across the world. So, these investments in rare disease are strategic investments in our healthcare system, but we do not think about it that way. We must struggle and fight for funds in the rare disease space and incentivize people to work in our spaces. We are not actually thinking about it as a public health investment.

**Mark Trusheim:**
We have made so much progress in science because the science was ready 20 years ago. As we began to understand the targets and went to a very mechanistic and personalized approach, progress was made. That is now possible for rare diseases. Through whole genome sequencing and other tools and techniques, we can now understand the mechanisms of rare disease in a much more tractable and rapid way than we could 20 years ago. Rare diseases are now ready for the same kind of explosion in progress that we saw in cancer 20 years ago.

**Erica Berg (host):**
*What I am hearing is that there seems to be a stigma around investing in rare disease research, potentially just because of the name "rare diseases" and I am curious to the origin of that. Mark, you mentioned a few times that people will sometimes respond with, "Well, it is a rare disease, why worry about that?" Is it just because they are rare or is there something deeper driving this perception that rare diseases are somehow less important?*

> ***"We are now seeing more regulatory pathways that are tailored to rare diseases, but we still need more predictability and certainty around those regulatory pathways. We also need more predictability and certainty around the access environment and what the reimbursement pathway will look like for those approvals. That is how we are going to continue to incentivize development in rare disease."***

**Annie Kennedy:**
I would say it is less about stigma, and more about the uncertainty around what the regulatory and access environment might look like. We are now seeing more regulatory pathways that are tailored to rare diseases, but we still need more predictability and certainty around those regulatory pathways. We also need more predictability and certainty around the access environment and what the reimbursement pathway will look like for those approvals. That is how we are going to continue to incentivize development in rare disease. So, from my perspective, this is not about stigma, it is about being able to strengthen those development pathways and, again, de-risk the investment. The other piece, as I said at the outset, is that we also need the resources to be able to identify who has a rare disease, to diagnose those who have a rare disease, and to build those resources and that infrastructure to support this work. That is an important part of de-risking the rare disease environment.

**Erica Berg (host):**
*Hadley, I was hoping you could weigh in on the ethics. What kind of weight can moral or ethical arguments carry in terms of persuading pharmaceutical companies, research organizations, or grant funding agencies to commit resources to rare disease programs?*

**Hadley Stevens Smith:**
That is a great question, and I think it also relates to the conversation that we were just having. One of the areas in which we see a lot of new and exciting investment is in genomic newborn screening. There is a new initiative from the NIH called the BEACONS program. The state of Florida has also devoted funds to start up a Sunshine Genetics program, where every baby in the state of Florida, and across several other states, as part of the BEACONS program, would have access to genomic newborn screening. Mark was highlighting the potential equity implications

of expanding access to newborn screening in this way. I think one of the things that we need to be careful about is balancing uptake with ensuring the program is designed in a trustworthy way, particularly when it comes to considerations around commercialization of the data and access to the sequencing data by companies that could potentially use it to develop therapeutics for rare disease. We must balance what the community expects from a trustworthy program with how we think about broader population benefits that could come from scientific and therapeutic advances. In the newborn screening space more broadly, I do think that we are seeing investment, along with the impact of the equity argument that access to a rare disease diagnosis early in life should be equally available to all babies across the country. That access does not only result in savings to the healthcare system and help eliminate the diagnostic odyssey, but it can also serve the pharmaceutical industry and the patients who would benefit from advances in rare disease therapeutics.

**Erica Berg (host):**

*Would anyone else like to weigh in on where these ethical obligations should play a role in this discussion?*

**Ulf Persson:**

I would like to add that sometimes we do have a budget there to pay for the investment. The bigger challenge is when we do not have any budgets available and we just have to pay for the improvement directly. When we are talking about the health improvement, we are used to paying for extra life years, life extensions and for improved quality of life. When we are dealing with orphan drugs and orphan diseases there might be a lot of other additional value drivers. For example, the degree of severity of the conditions, which are often very severe. Sometimes the goal is to reduce the risk of disease progression, and there is what we used to call the "value of hope", paying for a chance that the patient might be one of those who respond to it, even if they are not the average people who respond to a certain treatment. This brings up new discussions about the value of risk reduction.

So, it is about considering risk reduction and sometimes accepting additional risk in cases where we have a severe condition. We must learn how to better evaluate these kinds of conditions. I am somewhat hopeful because there is a lot of ongoing research, much of it from the United States, which we are using in Europe. Many times, some of these researchers in the US are a little ahead in understanding how to acquire new evidence about patient preferences for different value drivers and get that evidence into the decision-making process for the payers and the Health Technology Assessment (HTA) organizations. They must take on these very difficult decision-making processes and get this new evidence of value into them. I think that is very important. This means we need to develop our value-based reimbursement system so that they can work for orphan drugs. There is still a lot of work to do in this area.

**Mark Trusheim:**

A positive trend is the increased emphasis on wellness and health, with early diagnosis and understanding people's risk as an essential part of acting as early as possible. It used to be that until you presented with something debilitating, the healthcare system did not pay too much attention. And from a research standpoint, there was not much attention given either. I think this shift is incredibly important. You are seeing it in cancer with early screening, and you are seeing it with newborn screening. That is a positive trend. I think it helps counterbalance the challenge that, as Annie mentioned, many rare disease costs are ignored because they are borne by families rather than the healthcare system. Unfortunately, for the most severe cases, death has historically been "cheap". Dying quickly from a rare disease does not cost much to the healthcare system. It therefore does not get built into how much we think we ought to spend for healthcare. I think we would be naive not to say that there is also a tension between people who do not want to see their health costs and their premiums go up as we expand. Luckily, we are getting better at treating other conditions more cost-effectively. On the drug side, I think the numbers are something like $200 billion or more in drugs that are coming off patent over the next five to ten years. That is a lot of drug spending that could be freed up for these kinds of new therapies. So, it is a great time to start swapping resources from other areas to rare disease, as those other conditions are now going to be cheaper to treat.

**Erica Berg (host):**

*I would now like to shift to a more forward-looking discussion. How can we foster a more collaborative environment between rare disease communities, encouraging collective progress rather than competition for scarce resources?*

**Annie Kennedy:**

I think that in the rare disease space we already have an incredibly collaborative environment, compared to other spaces. I think this is because it does take everybody rolling up their sleeves and working together towards a shared mission, as well as an unparalleled amount of passion to dedicate towards discovery for a specific rare disease. Oftentimes, communities are convened by a patient community or a group of patient communities, so the spirit of collaboration runs deep and strong in the rare disease space. I do not think that the competition in rare is negative. I think it is probably why it fuels rare and it does not detract from the mission and the goal. I do think that we need more enhanced incentives and that we need to protect the incentives that we currently have in the rare disease space. This will help ensure that the investors and the developers already engaged in rare remain, while attracting those who are maybe standing on the sidelines into our space. Additionally, we need incentives to draw the best and the brightest in the scientific, payer, and diagnostic fields into our rare disease space, because that is what we need now more than ever.

**Erica Berg (host):**

*I guess I was thinking more along the lines of collaboration beyond the rare disease communities, so more about getting at this tension between common conditions and rare conditions and this battle for resources. Hadley, could you share some thoughts?*

*"In the rare disease space, we know that we often have highly motivated patient communities who are also very generous with their time. It is a true honor to be able to carry out research with rare disease communities because they are so motivated to work together and to share their stories and to move the field forward. There is always an altruistic motivation that is apparent in working with these communities."*

**Hadley Stevens Smith:**
Annie makes a great point about collaboration within rare. I also think that we can go back to this idea of the scientific spillover effect. So, what can the broader medical community or the broader basic science community learn from what is happening within rare disease? On the academic side of things, we often think about what we can learn from rare disease patient populations, particularly in terms of improving methods for understanding patient-centered outcomes. Those learnings can then be translated into these broader disease spaces as well. I think that it really comes down to decreasing and breaking down silos and being more collaborative, especially around the efficiency of learning across different spaces. In the rare disease space, we know that we often have highly motivated patient communities who are also very generous with their time. It is a true honor to be able to carry out research with rare disease communities because they are so motivated to work together and to share their stories and to move the field forward. There is always an altruistic motivation that is apparent in working with these communities. So, I think taking what we have learned about how patient engagement science works in rare disease and translating that into the broader medical sphere is an important take away from this experience.

**Ulf Persson:**
I can see concern about a new conflict that has emerged recently in my country and in some other European countries. It is a conflict between budgets for treating common diseases like diabetes, obesity, and Alzheimer's disease with the new drugs coming onto the market, and the budgets for orphan diseases. Sometimes the argument is that if we pay more for treating the orphan diseases, we will have to reduce spending on diabetes, obesity, and Alzheimer's disease, or whatever else is coming next. I understand the discussion, but at the same time, when we are talking about common diseases, we are talking big budgets. When we are talking about the orphan diseases, we are often talking about very few patients, even in if the price per patient may be high. But we are not talking about the same kinds of budgets. I think there must be some other criteria to justify the pricing for orphan disease treatments instead of evaluating them on risk reduction in the same way we do for common diseases, even though those are very important for the prevention of future diseases related to overweight and similar conditions. I understand the logic, but this is a direction of discussion that I am not very comfortable with, even if I can see where it is coming from.

*"If we could track symptoms with the same rigor that we track billing codes, we would have a data infrastructure that everyone, from scientists to payers, could leverage in phenomenal ways. That represents a huge opportunity but requires collaboration across many of these stakeholders."*

**Mark Trusheim:**
There is a clear need for data infrastructure, from natural history studies onwards. We know that Medicare and increasing numbers of other payers want to pay based on outcomes and that requires a quantitative understanding of patient experience, patient status, and where patients are at any point in time. We have a huge billing system where we track all the inputs with excruciating detail, but we collect very little data about how the patient is feeling, what their symptoms are, and what their actual functioning is in daily life. We do not collect that information systematically in the healthcare system. That would seem to be the basis for understanding real value across large population diseases and rare diseases. It would allow us to understand the natural history of all the subtypes of obesity, diabetes and cardiovascular disease as well as the thousands of rare diseases. That kind of understanding is simply not the way we practice care and or manage health today. The FDA and NIH should be commended for the many rare disease registries they have funded over the past five years. They are in the dozens if not the low hundreds at this point. However, they are all one-off efforts. They are not part of a systematic approach to tracking the data on how well patients are doing once they encounter the healthcare system. We still lack a way to understand their symptoms and track them just as rigorously as we track how many billing codes we can put in the medical records. If we could track symptoms with the same rigor that we track billing codes, we would have a data infrastructure that everyone, from scientists to payers, could leverage in phenomenal ways. That represents a huge opportunity but requires collaboration across many of these stakeholders. It is a fantastic opportunity for us, particularly with the use of AI, as long as we follow clear rules about the appropriate and ethical use of all this information.

## Building a global community for rare disease: Accelerating treatments, access, and collaboration

Rare diseases affect millions of people worldwide, yet patients and families continue to face unequal access to diagnosis, care, and emerging therapies. Strengthening a global rare disease community—uniting researchers, clinicians, policymakers, patient advocates, and data leaders—is essential to reducing these disparities and accelerating meaningful progress.

This panel will explore how international collaboration can advance rare disease research, improve care pathways, and address long-standing inequities across regions. Discussion will focus on the importance of shared data, coordinated policy efforts, and patient-led initiatives, as well as the opportunities and challenges posed by diverse healthcare systems and regulatory environments. Ultimately, the session will examine how collective action across borders can accelerate solutions and improve outcomes for people living with rare diseases worldwide.

Participants will:

- Understand how global policy and advocacy efforts can reduce disparities in diagnosis, access, and care.
- Recognize the role of international registries and data sharing in advancing research and empowering patients.
- Explore strategies that organizations can use to build capacity and drive rare disease progress across diverse health systems.

## Panelists

**Benjamin Forred, M.B.A.**
**ZebraSite Studios, South Dakota, United States**

**Roberto Giugliani, M.D., Ph.D.**
**Federal Universit of Rio Grande do Sul, Porto Alegre, Brazil**

**Eda Selebatso, Ph.D.**
**Botswana Organisation for Rare Diseases, Gaborone, Botswana**

**Rachel Smith, B.A.**
**Parexel, United Kingdom**

**Erika Gebel Berg, Ph.D.**
**Science/AAAS, Washington, DC; moderator**

## The Conversation

**Erika Berg (host):**
*Rare diseases affect millions of people worldwide, yet patients and families continue to face unequal access to diagnosis, care, and emerging therapies. Strengthening a global rare disease community by uniting researchers, clinicians, policymakers, patient advocates, and data leaders is essential to reducing these disparities and accelerating meaningful progress. Today we will be exploring how international collaboration can advance rare disease research, improve care pathways, and address long-standing inequities across regions. I would now like to take the opportunity to welcome our panel today.*

**Eda Selebatso:**
My name is Eda Selebatso. I am from Botswana and I am also based in Botswana. I am a mother of two children with rare diseases, the oldest with an undiagnosed kidney disease, who had to undergo a kidney transplant at the age of 6 and who is now 17 years old, and a daughter with Morquio A (also known as mucopolysaccharidosis type 4A). We received her diagnosis when she was 3 years old, after sending her samples to NHS Manchester in the UK. That basically sets the stage for where we live and what access looks like for us. Therefore, due to my personal challenges, I established an organization for rare diseases to make sure that we could reach out to other families struggling with the same issues that we have had to grapple with. I have been in this space for over 10 years. I am not only doing work in my own country; I also have responsibilities globally where we collaborate with other international organizations focused on rare diseases and I serve on different boards.

**Rachel Smith:**
I think this proves how small the world is. I am actually in the UK and I am just south of NHS Manchester, so I am very familiar with the rare disease work that they do. My name is Rachel Smith and I am currently working in the clinical research space at Parexel, as the Vice President and Head of the Rare and Genetic Disease Group. I work in global drug development, and I do truly mean global. I have worked very closely with the Middle East, Africa, India, China and most of the APAC countries, as well as Europe, North America and Latin America over the course of my career that now spans two decades. I am also a rare patient myself. I have a rare blood condition and it took me quite a while to get diagnosed, despite working in this field and despite working with advocacy groups. I was familiar with the patient journey and knew the signs and yet I struggled to identify them in myself. I am based in the UK, so you would think that it would be an easier diagnostic path for me. It unfortunately was not, so I am really thrilled to speak about the global approach to rare diseases today.



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**Roberto Giugliani:**
I am Roberto Giugliani. I am a medical geneticist based in Porto Alegre in the south of Brazil and I am a professor at the Federal University of Rio Grande do Sul. I also work in the University hospital as a medical geneticist and I am a consultant for Dasa Genomics. I am now the director of a new rare disease center, which is called Casa dos Raros (House of Rares in English), which was established a couple of years ago and is developing some innovative actions in the field of rare disease.

**Benjamin Forred:**
My name is Ben Forred. My background is in cell and molecular biology. I spent about 15 years as a researcher working at a large academic hospital system in the United States and I have done rare disease research at the bench, but I have also helped lead a team of clinical researchers on our genetics, genomics and rare disease portfolio. I also directed the Coordination of Rare Diseases at Sanford (CoRDS) Rare Disease Patient Registry for about 10 years.

**Erika Berg (host):**
*I am going to put this first question to all of you. Across the entire range of rare disease research and care, which parts benefit most from having a truly global and inclusive approach?*

> ***"When you are somebody who is located in a place like Botswana, and this applies to the whole continent of Africa, resources are limited and you find that other countries with resources are way ahead when it comes to rare disease research. However, this does not mean that the resource-limited countries have nothing to offer."***

**Eda Selebatso:**
When looking at research and even care, I would say that they would both benefit from a truly global and inclusive approach. I will start with research. When you are somebody who is located in a place like Botswana, and this applies to the whole continent of Africa, resources are limited and you find that other countries with resources are way ahead when it comes to rare disease research. However, this does not mean that the resource-limited countries have nothing to offer. You soon realize that research informed by local findings, misses insights that could be learned from places like Africa, which has a large population and could play an important role for things like clinical trials. Even though little is currently being done, there is a huge opportunity to gather a great deal of valuable information. This is especially true because there are lots of differences in our populations. Our cultures, our environments, and our genetics are different. Therefore, there is value in looking at other places even though there might not be resources available.

When it comes to care, there is also an opportunity to collaborate and exchange information. For countries without much information on rare diseases, there is no need to start from the ground up. There is already information out there that could be shared and could benefit the patients. There could also be a sharing of the rare disease specialists, who would benefit by taking care of patients that they would not naturally encounter in their usual care settings through the use of technology. The countries that do not have such specialists would also benefit and that access could then be made easier.

> ***"If you are only looking at 20 patients in the US or five patients in the UK, you do not get a representative understanding of what that condition or its natural history looks like and without that, we cannot know what we need to focus on to treat it."***

**Rachel Smith:**
When it comes to rare diseases, we are talking about very small populations within each country, but together they are not. The number of rare diseases changes every day, depending on what source you look at, and that is a part of the problem because we do not know how many people are impacted by rare diseases. So, we really need to work globally. If I was going to highlight one thing, it would be data sharing. About 80%, or potentially even more than that, as we are identifying more and more rare conditions every day, are genetic in nature. So, we have all of these genetic variations and different phenotypes. If you are only looking at 20 patients in the US or five patients in the UK, you do not get a representative understanding of what that condition or its natural history looks like and without that, we cannot know what we need to focus on to treat it. A lot of these conditions are also multiorgan and multisystem diseases and so, not just affecting the skin, kidney or brain. We are really looking at global conditions. By bringing all of that data together, from Botswana and all over Africa, China, and India, and integrating it with European and American data, it will allow us to have this full understanding of what the solution looks like. We will be better able to understand how to treat the disease, which will lead to more research opportunities and the development of more drugs. For me, that is the key piece.

**Roberto Giugliani:**
I can give many examples, but I will focus on one that occurred a few weeks ago. We had a conference on undiagnosed diseases and it was organized for the first time in the Southern hemisphere in Latin America. It took place in Rio de Janeiro in Brazil. We had around 400 people from 45 countries discussing how to approach patients with an undiagnosed disease. This is because often we perform an investigation to identify the disease and to make the diagnosis, but we do not always reach a conclusion. This patient, therefore, remains without a diagnosis and without a diagnosis it is difficult to receive proper treatment and management. So, it is very important to have a diagnosis. In

developed countries, and especially in the US, Canada, Europe and Japan, there are programs for undiagnosed diseases, but most lower- and middle-income countries do not have these types of programs. So, we have now established Undiagnosed Diseases Network International, which aims to disseminate this kind of approach and tries to expand the possibilities of making a diagnosis in patients with a rare disease. We had this conference and, as a result, many countries established their own undiagnosed disease program. This is an example of how international collaboration can advance the field.

***"As a person who lives with a rare diagnosis, I can tell you that we all start as undiagnosed and so, we know how that feels, and we also know what it feels like to get an answer, even if it is not one that you are really happy about."***

**Benjamin Forred:**
A lot has already been touched on, but I think there are two things that jump out at me in terms of global impact. One would be advances in genetic testing globally. The more genetic testing we can do, the more we can understand the human genome across all of our differences, including in race, gender and wherever we are on earth, and that will help eliminate variants of unknown significance (VUSs) and understanding more about how systems play together. The other major point is the advances that are being made in data science, where we are taking all this healthcare data from different systems, countries and places, and then finding common models that can be used to organize that data so that it can be analyzed across all sorts of different contexts. We are now getting to a point where we can take a global approach at looking at what makes us sick. As a person who lives with a rare diagnosis, I can tell you that we all start as undiagnosed and so, we know how that feels, and we also know what it feels like to get an answer, even if it is not one that you are happy about. So, I think that the advances in data science, genetics, newborn screening, and similar things are going to have a huge global impact.

**Erika Berg (host):**
*Roberto shared a brilliant example of where international collaboration is making a difference. Does anyone else have any other examples they would like to share of a recent experience where international collaboration really demonstrated the power of what working together can do for rare disease?*

**Benjamin Forred:**
I have been working with the International Rare Diseases Research Consortium (IRDiRC) and have been on a task force for preventive medicine for the past year. About a dozen of us have been meeting regularly to put together a white paper about different approaches globally that can be taken in regard to preventive medicine for rare disease, which is an interesting thing to wrap your head around. That has been a really great task force that has come together across different continents and different backgrounds to understand that there is not really a one-size-fits-all solution. Being nimble and being flexible is going to have to be a major component of moving the needle and advancing research for rare diseases globally.

***"This year we were very fortunate to collaborate with the European Commission and EURORDIS, with an initiative called EU-X-CT, which is essentially opening up cross-border enrollment to increase access to clinical trials. This means that even if you are not located in the country where a clinical trial is being run, you can still access the clinical trial and its treatment options."***

**Rachel Smith:**
I have a couple of examples. To add to Ben's earlier point, I think there is so much going on in this space. There are so many groups that are either individually or collectively working together. So, you have the N of 1 space where there are individuals that are not usually N of 1 when we start looking closer, but they start off that way. Then we have basic examples from the clinical space. This year we were very fortunate to collaborate with the European Commission and EURORDIS, with an initiative called EU-X-CT, which is essentially opening cross-border enrollment to increase access to clinical trials. This means that even if you are not located in the country where a clinical trial is being run, you can still access the clinical trial and its treatment options. We are often working with patients with these really rare diseases and conditions and we are opening a site in Canada and in Germany and the patients are located all over the world.

We had a patient recently, a young boy, who lives in Kazakhstan and we were very fortunate to be able to link him with an investigation from a site in Germany and actually had that patient enroll in a 12-month clinical trial where he opted to stay in Germany for those 12 months. That would not have been possible if we did not have the guidelines and the regulations in place that allow for that kind of access to healthcare in the clinical trial setting. So, that guidance is really benefiting patients. That is one case in particular, but we have hundreds of these patients in clinical trials where it is not in their home country, which is amazing.

**Eda Selebatso:**
I will touch on three things that have tremendously impacted patients' lives. Diagnosis is a big one, as we do struggle with diagnosis in this part of the world, especially with rare diseases. As Ben has said, genetic testing is the most important tool for reaching a diagnosis but there are infrastructure limitations that affect access to it. So, we have collaborated with Genetic

Alliance to continue how we have been collaborating globally to get a diagnosis. The difference is that we are now able to get more patients treated through the iHope program, which is spearheaded by Genetic Alliance. Without such collaborations, we would not be able to go further with a diagnosis. Secondly, in regards to treatments, our government in Botswana does not offer treatment to patients with a lot of these conditions because of the costs. Therefore, we have some patients that have been treated through charitable access programs that we are involved in. In terms of policies, a lot of our countries do not have policies that are specific to rare diseases. But we are aligned with international organizations. We are happy that the recent World Health Assembly (WHA) Resolution on Rare Diseases has been achieved and we have been a part of that process as representatives from Botswana working with other countries. So, these types of collaborations are very important because once you have something like this WHA resolution, you have a base on which to start and continue conversations and have guidance for all countries on how to approach the policy issues.

**Erika Berg (host):**

*What are the biggest gaps that you see in rare disease resources between high-income countries and the rest of the world? Is it in diagnostic testing or is there something else you are seeing?*

> ***"When it comes to access to treatment, I think there is an even bigger gap between high-income countries and low-income countries because the access to these expensive therapies is very limited. There are some charitable programs that contribute a little to decrease this gap. However, we still require some innovative solutions for this issue, as it will not be possible for middle-income countries to face the cost of some of these expensive therapies."***

**Roberto Giugliani:**

I think there are many large gaps and diagnosis is one example. It was already mentioned, but access to diagnostic tests is still very limited in low- and middle-income countries, and this is a major challenge. In Brazil, we are establishing a kind of collaboration where we raise money so that we can offer diagnostic tests for several diseases to countries in Latin America that do not have them available. Now, with the use of dried blood spots and urine-impregnated filter paper, we can ship these samples without ice or a cold chain, making it easier to cross borders and support this international collaboration in terms of diagnosis. It was already mentioned, but when it comes to access to treatment, I think there is an even bigger gap between high-income countries and low-income countries because the access to these expensive therapies is very limited. There are some charitable programs that contribute a little to decrease this gap. However, we still require some innovative solutions for this issue, as it will not be possible for middle-income countries to face the cost of some of these expensive therapies. There are some alternatives that we can discuss later on.

> ***"At the Botswana Organization for Rare Diseases (BORDIS), one of our objectives is to ensure that, wherever resources allow and opportunities exist, we work with our doctors to help build their capacity. This includes not only doctors, but other healthcare providers that offer support for the care of our patients."***

**Eda Selebatso:**

Besides what we have already mentioned, there is also the capacity gap among healthcare providers. It is a huge gap and it is very critical to how you first get diagnosed, because it is very much hinged on the doctor's index of suspicion. If someone has never encountered a rare disease, or that particular rare disease, it is going to take a long time for them to eventually prescribe the test needed for a diagnosis. At the Botswana Organization for Rare Diseases (BORDIS), one of our objectives is to ensure that, wherever resources allow and opportunities exist, we work with our doctors to help build their capacity. This includes not only doctors, but other healthcare providers that offer support for the care of our patients. We have actually hosted two trainings for African doctors in Botswana, and after those trainings, we have seen a tremendous increase in the number of lysosomal storage disorders being diagnosed. So, that is one important issue that still needs to be worked on.

**Erika Berg (host):**

*Ben, when it comes to improving capacity in countries with fewer resources, what kinds of investments in training, technology, and infrastructure can create the biggest improvements for rare disease care?*

> ***"Being able to have a patient receive a diagnosis is one thing, but to have a family understand what that diagnosis means is another. When you are talking about rare disease, receiving that diagnosis is too often the end of the conversation."***

**Benjamin Forred:**

That is a great question, and it might sound like a cop out, but I think it is a combination of those three different things. You need to have the infrastructure in place. If we take something like newborn screening, you need the hospital systems and the professionals to have the ability to order the tests, have them sent out, get the results sent back, and then have people there to an-

alyze them. There is also a necessary component of that which is focused entirely on healthcare literacy. Being able to have a patient receive a diagnosis is one thing, but to have a family understand what that diagnosis means is another. When you are talking about rare disease, receiving that diagnosis is too often the end of the conversation. There is not a, "And this is what are we going to do about it" portion. Only 5% of rare diseases have any kind of therapy or approved treatment available. So, you are stuck trying to fight symptoms instead of a root cause. You need to have a strong health literacy program, with either the help of genetic counselors or social workers at the hospital, so that people can understand how this is going to impact their life and what resources are available to support them. Without the ability to test people and then effectively help them manage their lives, you are not going to have the impact that you desire.

**Erika Berg (host):**

*Rachel, we often hear about these collaborative efforts, such as IRDiRC, that are looking to help rare disease communities globally. In your experience, how are these collaborations speeding up research and improving access to care?*

> ***"We have some great examples from the COVID-19 pandemic where vaccine programs globally were partly funded by those higher-income countries to give access to the vaccines, when they were available, to lower- and middle-income countries. I think something like that would be really helpful for rare diseases."***

**Rachel Smith:**

The biggest thing they do, and IRDiRC is a great example of this, is they shine light on rare diseases. To follow up on Eda's point, the fact that we have the resolution recognized by the World Health Organization was absolutely huge because that was really the recognition of what we have all been saying: that rare is not rare and you do need to have a global and international approach to it. I think IRDiRC has done an amazing job along with C-Path, EURORDIS and other organizations that are either cross-country partnerships or broader collaborations aimed at improving research. So, they are improving awareness around rare diseases. If the symptoms seen together do not make sense, then it is probably a rare condition and we should go ahead with some sort of genetic testing. So, there is a need to increase the access to those sorts of tests. Georgia is an example of a country where we work quite frequently and they have a partnership with a lab in Germany to do all of their genetic testing and that has reduced the time it takes to access that data and access those results. That is really important because they do not have the infrastructure themselves to do that testing. A lot of that has been possible due to the national and international organizations building the guidance, policy and regulation changes, and making access to those things much less difficult. I think also harmonization and guidelines are important. Yes, there will be local healthcare system and regional differences, but ultimately rare conditions as a whole have a lot of commonalities and they are really heterogeneous. We are talking about small populations in the individual countries, the delays to diagnosis, and the lack of access to research or to approved drugs. Being able to put frameworks and best practices in place allows countries like Botswana to say "There is a framework here for us to work from." They may not be able to implement everything and these pieces may not make sense for their healthcare system or they may not be able to fund them, but I think having those pieces of data is really important. The other piece for everybody is the funding. We have some great examples from the COVID-19 pandemic where vaccine programs globally were partly funded by those higher-income countries to give access to the vaccines, when they were available, to lower- and middle-income countries. I think something like that would be really helpful for rare diseases. These organizations have funding programs to look at implementing certain task forces or infrastructure in those countries or giving them access to infrastructure that already exists in another country. So, that funding is sporadic, it is there, but it is not on the global scale yet. But again all, of this has really advanced research. IRDiRC, as mentioned, is a great example because we have had over 100 therapies that have been notably accelerated as a result of that organization independently. Obviously, there were many more examples, but that gives us a very clear figure.

**Erika Berg (host):**

*Roberto, can you tell us more about the Rare Disease International (RDI)-Lancet Commission on Rare Diseases? What are your hopes for how it might shape global rare disease care?*

**Roberto Giugliani:**

The RDI-Lancet Commission on Rare Diseases was established last year, and it came after the UN resolution about making rare diseases a global health priority. We realized that it was important to organize the view of the international community about rare diseases. So, we formed a commission comprised of 27 commissioners coming from different countries, with all continents as well as high-, low- and middle-income countries represented. We are currently discussing how to present this topic of rare disease, to set the scene for the WHO.

In 2025 the World Health Assembly approved a resolution designating rare diseases as a global health priority and now the WHO will establish guidelines for the member countries about rare diseases. So, we decided to form this commission, and we formed five working groups. One is focused on the ethical and moral aspects. Another is focused on the data and metrics, because when we talk about 6000 or 8000 rare diseases, we should really look at these numbers and be able to provide evidence when we say 70% or 80% are genetic. We also have a working group on societal and healthcare systems to approach the diagnostic odyssey of these patients. There is equally a working group on clinical pathways to examine the therapeutic alternatives. Finally, there is a fifth working group on healthcare professional competency. The importance of having these healthcare profes-

sionals trained in rare diseases was already mentioned. These are the five working groups that are working hard to produce documents that I think will be very instrumental for the people working in these areas and especially for the WHO, who should issue some resolutions and guidelines in the next years about rare diseases. So, I think we are in a very important moment, and the RDI-Lancet Commission on Rare Diseases will provide some important information and evidence for these documents that should arrive in the coming years.

**Erika Berg (host):**
*When will we get these documents? I know it is a work in progress, but do you have a sense of when they might start coming out?*

**Roberto Giugliani:**
We published a very brief document earlier this year stating the foundations of this Lancet Commission. It was published in *The Lancet* in the February 2025 edition. The five working groups are currently working in parallel and I think we should have a final document for publication in early 2027, because we will take all next year to finalize our work.

**Erika Berg (host):**
*I am going to switch gears a little to talk about patient registries, which are central to rare disease progress. Ben, what advances have you seen in making these registries more globally representative? Could you maybe talk about why they are important, your role in the CoRDS Registry and how that fits into these efforts for building these registries?*

> ***"I think the biggest success that we have had is in making sure that regardless of what language a person speaks, where they live or their economic status, they are freely able to contribute and tell their story via the CoRDS registry. That is something that I personally feel really proud of."***

**Benjamin Forred:**
The first thing I will say is that in rare disease, everyone has to acknowledge that the experts in the room are the people living with the disorders. So, to start making progress anywhere, you have to let them tell their story. A registry is at its core a tool. It is a set of questions built on a collection of demographic and contact information, which allows for the longitudinal gathering of data as life goes on for rare disease patients. Across the community as a whole, you can identify things that are common. Just looking at my experience with the CoRDS Registry, I could provide many examples of how researchers, who have spent a lot of time focused on a given condition or a given organ system, were able to identify new symptoms or pathways involved in a given rare condition because of the registry data that was collected from that community. One of the most important things that has been done to make registries more approachable internationally is the understanding that ICD-10 codes and the way we classify disorders were designed for billing purposes and using them for research purposes can be a little ham-fisted at times. So, there has been a lot of work done to try to find ways to consistently label a given disorder so that across systems you can understand that we are talking about the same thing. One of the groups that has been very influential in this area is Orphanet with their ORPHAcodes and their list of rare diseases. We are now able to assign a number to a given diagnosis, which may go by 30 names across the globe but we understand it is the same entity. We need to be able to refer to a diagnosis consistently in a research setting, so that has been a huge accomplishment.

In terms of CoRDS, I think that when it started it was about recognizing and understanding that there is no easy way for people to access research and to overcome that initial hesitation about participating. There have been enough researchers behaving badly over time to give people good reason to be a little skeptical. So, there is this layup situation, where patients can participate in research early on and we basically said that we would try to create registries for all rare conditions and understand how that works. Our biggest challenge in the beginning was finding people. It is really hard because there is no directory and rare diseases do not obey geographies or languages or races or anything else. So, you must look at the entire world. We took the approach of partnering with advocacy organizations and patient groups around the world that are focused on serving their local communities and making sure that their people have the resources they need. We might not know where everyone is, but those groups do. So, over a period of about 10 years, we partnered with 150 to 200 different advocacy groups, and we built them free registries so that from an early stage they could begin collecting structured data under an IRB protocol. This ensures that proper consent is in place, people understand what they are getting into, and that registry data can then be used down the road for any number of things. I think the biggest success that we have had is in making sure that regardless of what language a person speaks, where they live or their economic status, they are freely able to contribute and tell their story via the CoRDS registry. That is something that I personally feel really proud of.

**Erika Berg (host):**
*Building trust for these patient registries is essential. Eda, what is your experience with patient registries and how do you make sure patients, especially those in resource-limited settings, feel confident about participating in patient registries and see the potential benefits of the research that might follow?*

***"Trust is built at the local level. For international registries, work has to be done with patient organizations that are in the specific countries or regions, and it does not just start with a registry."***

**Eda Selebatso:**
Though we do not have any registries in Botswana and there are a limited number of country-specific registries in Africa, we do contribute as rare disease patients to international disease-specific registries, as Ben has just mentioned. Trust is built at the local level. For international registries, work must be done with patient organizations that are in the specific countries or regions, and it does not just start with a registry. What builds trust, in my experience, is that as we work with patients for things that are care-related, you interact with them and their data. The way you deal with their data builds trust. How you deliver on things that they are expecting from you builds trust. So, whenever you say, 'we are now starting registries,' that trust has already been built through the day-to-day engagements related to care and the other social aspects of their lives. Because at BORDIS we say that rare diseases are not just a health issue, they affect every aspect of a human's life.

So, that is how trust is built, from the very beginning. Then, the patient organizations are just a trusted bridge for the patients to say they can participate in the registries. I have worked with different patients that have said, "I have seen this registry that is related to my condition. Is this a good thing to do?" What we do is we sit down and talk about it and share the objectives so that they can see how they are related to their conditions, even if they might not necessarily benefit from it directly. They then start to see how it relates to their own condition and to their wider community. It is not just about contributing for a direct personal benefit, but you also look around you and consider what this information can achieve in the long-term. It is also important to outline how their data is going to be handled and the control that they have over their data. Will they be able to remove their data if needed? Who is going to use their data? Who is going to look at their data? These are the issues that are very important when we discuss registries with patients and having the patients very much involved is critical to building registries.

**Erika Berg (host):**
*Rachel, I wanted to ask you what are some of the cultural, regulatory or technical barriers that still make data sharing difficult and are you seeing solutions that are giving you hope?*

***"Even in high-income countries like the US, there are real problems around that trust for data sharing and where that data is going."***

**Rachel Smith:**
I just want to add to what Eda said. Trust is based on communication and transparency, and that is the foundation for everything. If we can do that correctly, it makes everything a lot easier. What then stands in our way, as you alluded to, is the variability. I think data protection regulations are there for a reason. While I am in the UK, we were part of the EU when the general data protection regulation came in, so we are protected by that. The challenges we have are that data protection regulations vary by country. In some cases they are super minimal or even non-existent and that can really erode trust because we want to make sure that we are protecting every individual's health data, as it is extremely sensitive data. So, what we are collecting cannot be identified back to the patient. If you are considering the United States, for example, with the healthcare insurance question, we have challenges with patients not wanting to have genetic sequencing performed. This is because if the genetics come back with anything other than something related to the direct condition that the insurance company already knows about, it can affect their premiums and their coverage.

Even in high-income countries like the US, there are real problems around that trust for data sharing and where that data is going. Then you have the European Union, which in theory has a harmonized data protection regulation. However, the interpretation of that data protection regulation varies by country, and it also varies by region within that country. In some places, it can even vary by the institutional interpretation of that regulation. I will give you a great example. We had an Italian patient who wanted to take part in a clinical trial in Germany and we agreed. One of the main things that we needed to do was get that individual patient's data sent from their physician in Italy to a physician in Germany. That, in theory, should be a really straightforward endeavor. It happens all the time between referring physicians. So, why could it not happen in this setting? In this case, because the process was going to be so lengthy, the patient was going to miss out on the clinical trial if we went through these local data protection requirements. What we ended up doing was we had the physician print out this patient's notes, and as this is for an ultra-rare condition, the notes were significant. They had to print them off and the family had to physically take these paper notes all the way to Germany to give to the physician. This happened last year, when we have computer systems, electronic medical records, and all of these technological capabilities. There may sometimes be internet access problems, but I do not know many countries and regions where people do not have access to cell phones or basic technology, and there is still a major problem with sharing data between countries. So, for organizations interested in conducting research globally, sometimes it is just seen as too difficult and too complicated and it discourages them from doing that research and sharing that data. Even the European Reference Networks that were set up as a European, publicly-funded body have had problems building their own registries due to the GDPR. So, we have needed to find solutions for the patient advocacy groups so they can get around some of the barriers, but it has been really challenging.

I think that as we get into the AI world, and we are in the AI revolution right now, the utility of AI will become clearer as we understand a little bit more about digitization, data standards,

and effective guardrails. That is really important as there are limited guardrails in place for the implementation of AI at the moment. As that becomes clearer, I do think people will naturally become more literate in data and understanding what happens when your data goes into a system and that will naturally help to break down some of those barriers that we see.

**Erika Berg (host):**

*Eda, could you talk about your organization, BORDIS, and give us a little background about how it got off the ground, how you built networks with other global advocacy groups and then maybe talk about what role organizations like yours play in shaping clinical trials and how you think that role is evolving?*

> ***"Collaborating at an international level has brought us tremendous growth. It has also given us a lot to work with, because once you connect with people that have gone before you, the speed at which you progress on certain issues is much faster. You are already ahead because you are not starting from zero."***

**Eda Selebatso:**

Establishing a patient organization is deeply rooted in the local context. So, you deal with the internal requirements within your country first and then build from there. From my experience, I had to start locally, dealing with whatever investments we needed and complying with the regulations that we needed to meet. Once that was set up, we then went out to see who we could partner with and what international organizations were there for us to affiliate with. That is when we joined RDI, IRDiRC and other international organizations. Growth does not just happen because you are affiliated with someone. You affiliate with them with your objectives in mind and knowing what gaps you want to fill. Then, once you collaborate with them, you build and grow from there. That being said, collaborating at an international level has brought us tremendous growth. It has also given us a lot to work with, because once you connect with people that have gone before you, the speed at which you progress on certain issues is much faster. You are already ahead because you are not starting from zero. So, that has been quite positive for us.

You also asked about the evolution of patient advocacy when it comes to clinical trials. In the international organizations that we are affiliated with, I am sure people must always say, "Eda is always going to bring this up," but Africa is way behind. I always ask directly, especially when the pharmaceutical industry is in the room, and I say to them one by one, "You do clinical trials, why are we not having sites in Africa? Why is Africa only recognized when someone is looking for a market to sell their products?" I get different answers, of course. But in a nutshell our advocacy and our voices are not included when it comes to clinical trials, and it is up to us to bring them to our doorsteps. Africa can handle clinical trials. Some people may doubt this but I have worked in health research. We conduct clinical trials across the continent. There are institutions that are well-equipped with people that can handle clinical trials. So, I guess it is a matter of continuing the conversation and not just talking but showing people what could be possible if they partnered with us.

**Roberto Giugliani:**

I think this is a very important point about international collaboration in clinical trials. We just had a conference, organized by IRDiRC, the European Rare Disease Research Alliance (ERDERA) and RDI, to foster international collaboration in clinical research for rare diseases. The topic of Africa was mentioned, as well as other countries that do not usually participate but have patients and have infrastructure. We really need to strengthen these links because for rare diseases it is essential to collaborate on clinical development. Patients are dispersed around the world, so international collaboration is crucial. What was mentioned about registries is very important because one of the things that lead us to create the RDI-Lancet Commission was the need for increased visibility of rare diseases. Registries contribute to increasing this visibility and also pave the way for clinical research because when we know where the patients are this makes it easier to organize a clinical trial. So, this is something that is really very important. Registries also contribute to a better understanding of the natural history of the disease, which is essential when designing a clinical trial. We need to know about the natural history of a disease and this information can come from the registries. So, registries are important, international collaboration is important, and we should also increase the participation of countries in Africa, Latin America, and some parts of Asia in these trials.

> ***"Often it is the sites located outside of the US and Western Europe that are our highest performing centers. They enroll the most patients and their data quality is amazing."***

**Rachel Smith:**

So, firstly, I am going to be inviting Eda to all my meetings with the sponsors that we work with because I am consistently fighting to bring clinical trials to any region other than the United States, Canada, and Western Europe. It is an uphill battle. I think the default is always to go to those countries for various reasons. FDA requires certain amounts of data, and often we do get exclusions and exceptions for rare disease, but that is still the default. To add to Eda's point, there is a perception that the infrastructure is not as established in these countries; however, clinical trials can absolutely be performed to an extraordinarily

high quality. Often it is the sites located outside of the US and Western Europe that are our highest performing centers. They enroll the most patients and their data quality is amazing. It is only once pharmaceutical or biotech sponsors start to go to those regions that they suddenly have a light bulb go off and think why have we not done this before? But it takes a lot of convincing and honestly it requires some evidence and proof points to enable them to make that jump because they have to go back to their investors and their board and they have to justify why they decided to collect data in certain countries. Obviously, when it comes to rare diseases, there are unmet needs in every country in the world. So, we can run a trial in every country in the world and there is no reason why we should not. It is just about making people feel comfortable so that they can make that leap. As I said, Eda is welcome at any of my calls that I have with sponsors because I think she has made an incredibly compelling arguments for Botswana and Africa.

**Erika Berg (host):**

*What is one change that you would love to see that would make the international rare disease research and care community more equitable, more connected, and more inclusive for everyone?*

**Benjamin Forred:**

It may be a bit pie-in-the-sky, but I would love to see more of a global approval process. People with rare diseases have it hard enough. They did not choose where they were born and so, it should not be held against them from a policy standpoint. They are all prospective trial participants and future consumers of those treatments. So,it would be great if policymakers and industry were able to look, at least for rare conditions, at how we can get this approved in a better, more global way so that it can be accessed more equitably.

**Roberto Giugliani:**

I will highlight the initiative of RDI to establish a global network of rare disease centers. Our center in Brazil, for instance, is participating in this global network. So, we have the same patient-centered approach to diagnosis, care, training and research in rare diseases. We will also partner with other centers in Africa, Asia, and Europe that do similar things. I think we will learn from each other and we will grow as a community. I think this is a very good initiative that will make a difference in the coming years.

***"If we could have a system where any patient in the world with any condition could access the right specialists and receive the right therapies, that would be a dream."***

**Rachel Smith:**

This goes back to my initial point around data sharing. It is about acknowledging that individually we are rare, but collectively the word rare disease is in itself a misnomer. It is something that is actually an inaccurate description of the community as a whole. We use cancer as a collective, when individually certain cancers can be rare diseases themselves. I think that we need to expand the international recognition that this is a global burden and requires a global focus. The resolutions are great. I want to see action on those resolutions and I want to see changes implemented at a global level rather than just regional small changes that are not really moving the needle significantly. So, again, this is a little bit more pie-in-the-sky, but if we could have a system where any patient in the world with any condition could access the right specialists and receive the right therapies, that would be a dream.

**Eda Selebatso:**

It is a known fact that countries that are resource-strained cannot, in a short time, build the brick-and-mortar infrastructures that are needed to ensure that rare diseases are well taken care of. So, when I thought about this question, what came to mind, as Roberto has already said, was networking. The technology used for networking is growing rapidly and the networks already in place at RDI could be improved and enhanced so that a doctor located anywhere in the world, provided they have access to technology, could talk to an expert specialist who could assess the patient. Like this, the patient can get the help they need without us saying we cannot build this and that. So, we need to focus more on networking and strengthening our collaborations across the globe. That is where we could approach equity at a steady, or maybe increasing, pace.

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