

Uncovering Rare Disease

A series of conversations with
experts on rare disease

Volume 2

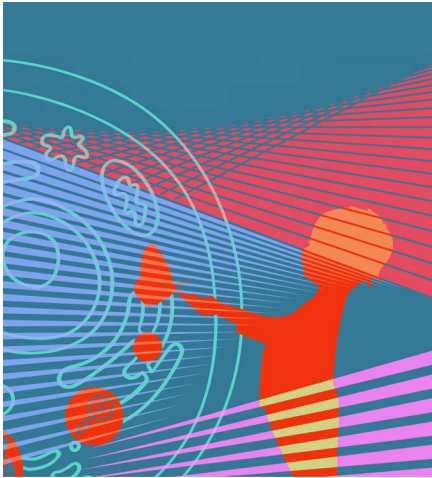


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Uncovering Rare Disease

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 forget 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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Reimagining rare disease detection: Who needs to be at the table?

Rare diseases pose unique challenges to the health care system. Unlike common diseases that affect millions, such as type 2 diabetes, a rare disease may have only 50 patients worldwide, spanning numerous countries, languages, and cultures. The detection of rare diseases—75% of which have a genetic basis—is generally difficult and costly, often requiring sequencing technologies that are hard to access. Physicians are frequently trained in the diagnosis and treatment of common disorders, but few receive instruction in rare diseases. The result is a diagnostic odyssey for the patient that often requires years of tests and specialist visits, sometimes ending without a clear diagnosis. The world's 300-million-plus rare disease sufferers are understandably anxious and frustrated, as are their health care providers.

Rare disease detection is an interdisciplinary and international problem. Building a solution must include internationally agreed-upon diagnostic criteria for each rare disease, patient access to diagnostic technologies, and effective communication strategies between health care workers and patients. In addition, relevant medical databases (e.g., patient DNA data) need to be international, multilingual, and readily accessible, crossing all socioeconomic boundaries. Academia, business, biopharma, artificial intelligence experts, international governmental agencies, and health care organizations will need to be at the table. Most importantly, patient voices need to be heard and honored, giving advocacy groups a central role.

In this webinar discussion, our diverse panel of thought leaders will tackle these issues and suggest a path forward for reforming and rethinking how rare disease detection and diagnosis is done.

Panelists



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Birmingham, AL



Avril Daly
EURORDIS,
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William A. Gahl, M.D., Ph.D.
National Institutes of Health,
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Charlene Son Rigby, B.A., M.B.A.
RARE-X,
Aliso Viejo, CA



Sean Sanders, Ph.D.
Science/AAAS, Washington, DC
Moderator

The Conversation

Sean Sanders:

Welcome to this first webinar in our 2022 Science and Life series on rare diseases, entitled Re-imagining rare disease detection: Who needs to be at the table?

William A. Gahl:

I am a pediatrician and a biochemical geneticist at The National Human Genome Research Institute at the NIH in Bethesda, Maryland. I study rare diseases and direct at the NIH Undiagnosed Diseases Program. I am also involved in some international efforts to bring Undiagnosed Diseases Programs to other nations.

Cristina Casanova Might:

I am the Executive Director for the Undiagnosed Diseases Network Foundation. We seek to end the diagnostic and therapeutic odyssey for all through the evolution and expansion of the Undiagnosed Diseases Network. I started my journey into rare disease advocacy as a parent of a child with a new NF1 rare disease. I am a rare disease patient now as well, so I am happy to be part of this conversation.

Avril Daly:

I work as the CEO of Retina International. It is a patient-led global organization of charities and foundations which fund and support research into rare forms of eye disease, retinal disease. I am also the Vice President of EURORDIS, which is the European Organization for Rare Diseases. I have worked on the development of policy actions around the issues concerning rare diseases for over 20 years now. I am also a person who is living with a rare disease: I am affected by retinitis pigmentosa, which is a form of inherited retinal degeneration. I am delighted to be here today to bring the European perspective to the discussion. Thank you for inviting me.

Charlene Son Rigby:

I am the CEO of RARE-X (<https://rare-x.org/>). RARE-X has developed a data platform to collect patient-reported data across rare diseases. I have spent my career building software solutions for the analysis of Big Data. Prior to RARE-X, I was focused on commercializing artificial intelligence technology to speed diagnosis of patients through genomics. I am also the mother of an eight-year-old girl, Juno, who has a rare neuro-developmental condition. She was diagnosed after a three-year journey, through whole exome testing. I co-founded the STXPB1 Foundation to advance development of treatments for kids like my daughter. So I am glad to be with all of you today.

Sean Sanders:

Bill, could you explain to us what defines a rare disease and how is "rare" differently defined around the world?

William A. Gahl:

In the United States, the 1983 Orphan Drug Bill defined a rare disease as one that affects fewer than 200,000 individuals. In Europe, however, the European Union defines a rare disease as one that affects fewer than one in 2,000 individuals. But that is for a single disease. If you consider the composite of all the rare diseases, it is a lot greater than that: estimates go anywhere from 300 million to 3 billion. So, when someone says that there are 300 million individuals in the world with a rare disease and there are seven billion people, it is about 5% of the population, or 1 in 20, whereas the definition in Europe, for example, is 1 in 2,000. So there is a two orders of magnitude difference. Of course, it is because there are a lot of different rare diseases, but a general estimate that is repeated in the literature is that there are 20 to 30 million people in the world with a rare disease. I think we should also consider all the individuals who are affected by having a person in their family, or an acquaintance, or a worker, or a boss, who has a rare disease. So numbers have incredible implications that affect all colleagues and family members of people who have rare diseases.

Sean Sanders:

Bill, do the numbers you mentioned include individuals who are undiagnosed? Is that an estimate of the number of people with rare diseases?

William A. Gahl:

Yes, it is just an estimate. How would we know how many people are undiagnosed? We might have an idea from genetics: there are databases that list variants, which are potential mutations, and one can estimate how many times, for example, for a recessive disease, some of the pathogenic mutations will come together to cause a rare disease. It is always true that the estimates based on those genetic variants are much greater than the actual number of people who are diagnosed. So it is clear that we are not coming even close to diagnosing all the individuals who have rare diseases—at least rare genetic diseases.

Sean Sanders:

Great. Cristina, would you like to share any thoughts, especially about the number of undiagnosed individuals? I feel like this is a really important part and something that we spoke about last year. We really don't have a good sense of how many people, both adults and children, might be living with rare diseases and never know it.

Cristina Casanova Might:

I think that is one of those things that we are currently trying to study along with the economic impact, because it is very difficult to make progress in this field unless we can quantify it and hopefully put some measures to it. That is something that we are very interested in. I would be interested to hear what Avril thinks as well, since I know that in Europe, there are some differences in this regard.

Avril Daly:

I think that the points that have been raised already show the complexity. We are looking at definitions that are so variable and different. We work in Europe on the assumption that there are 30 million people living in Europe with a rare disease and 300 million people globally affected by rare diseases. Rare Diseases International, which is an organization made up of patient advocacy groups that are working globally on all continents, is currently working with the WHO to look at an operational definition that is clear, and that we can work towards as a global community to overcome these challenges. How can we really define the effects of these conditions — not only on the patients in their day-to-day lives, coping with and living with a rare disease, but also the burden on society, on governments, on healthcare systems and what we need to plan for the future — if we are not aligned?

I also hope that through conversations such as this one, that include a broader stakeholder engagement and a broader geographical discussion, we can arrive at a solution, because it is currently a real burden for all of us. From my own perspective, working in an international organization with colleagues in different countries, it is hard, as advocates, to address this issue. So, yes, we are working towards that, and hopefully these discussions will further enable it.

Sean Sanders:

Great, thank you so much, Avril. Cristina, I just wanted to come back to you with a question about some of the psychological effects of living with a rare disease, and living with no diagnosis.

Cristina Casanova Might:

Absolutely. My son, as I mentioned, struggled with a rare disease, and for a long time, he went undiagnosed. He was one of the first cases of clinical exome sequencing in the United States and he was successfully diagnosed with a disease called NGLY1 deficiency caused by an error in the gene known as NGLY1. For those years, the anxiety, the stress, and the toll on our families and others was significant. The toll from multiple misdiagnoses that almost cost him his life was also significant, as well as the toll on our family and other relationships. This is repeated across the rare disease space, it is not unique to us. Actually, his rare disease led to my rare disease because living in an ICU for weeks and weeks at a time gave me an autoimmune condition. I now have generalized myasthenia gravis as a result of the stress on the caregiver. It is obviously not my son's fault. Unfortunately, he did not win his battle against rare disease, he passed away in October of 2020, just shy of 13 years old. The struggle that we faced here in the United States is replicated across the globe for patients, for their caregivers, and for others within the community. That stress is severe and is often comorbid with several psychological effects such as depression, anxiety, and other issues that come along, that can sometimes confuse the diagnostic process. The issue definitely needs to be addressed more holistically as we treat patients with rare disease. Oftentimes they are seen as a collection of symptoms rather than as a whole or as a person, as a family unit, and we really need to view things a little bit more holistically to be more effective overall and hopefully not waste as

many resources — especially time. I feel like in our country, we are very fortunate that there is not as much societal shaming or shunning as there are in some of our colleagues' countries, where there is a great deal of fear and isolation, more so than there even is here. It absolutely breaks my heart, but for rare disease patients in Africa, for example, they have been stoned because they don't have a diagnosis or because they have a rare diagnosis that is intimidating. So the more knowledge, the more insight, the more light we can shed on these diseases, the more acceptance there is. Even if there is not a treatment, at the very least, there is some humanity and some validation in that.

“That stress is severe and is often comorbid with several psychological effects such as depression, anxiety, and other issues that come along, that can sometimes confuse the diagnostic process.”

William A. Gahl:

We found in the Undiagnosed Diseases Program that when individuals can not put a name on their disorder, there is a lot of suspicion about whether they really have a rare disease or a disorder. That has an impact on their relationships with their family, their employers, employees, colleagues, etcetera. It also has an effect on their physicians. There are times when physicians, probably in part because they feel inadequate or because they haven't made a diagnosis, don't actually want to see the patient! We have noticed that for many of the patients who come to us in the Undiagnosed Diseases Program.

Sean Sanders:

Charlene, I would like to turn to you now since you have been through a similar odyssey to Cristina, and I am also interested to know how the work that you are doing at RARE-X impacts this diagnostic odyssey and particularly the misdiagnosis of rare diseases which can prolong the odyssey and cause a lot of pain and suffering.

Charlene Son Rigby:

We are building a platform that enables the collection of data across rare diseases. We felt that this was very important because to start the process for collecting data — to start to characterize a disorder — can be very expensive and complicated. This is often started by a patient advocate because there aren't researchers who are interested in their disorder because there might be vanishingly small numbers of patients that have been identified for that disorder.

We wanted to enable patients to be able to collect a robust amount of data in a robust and standards-based way. We have structured the platform in such way that we are not assuming that a patient has a particular diagnosis. This is important because for a lot of rare diseases, especially new ones, we don't know what all the symptoms are. Our goal with being able to have patients start to collect data is to do an initial characterization, and this

also enables us to address undiagnosed patients because they can start to categorize and catalogue what symptoms they are experiencing. We therefore build the body of data on the road to diagnosis.

Sean Sanders:

Bill, what are some of the most critical factors in the length of time to detection or diagnosis? Why does it take so long?

William A. Gahl:

One major issue is that physicians and healthcare workers are not familiar with a lot of the rare diseases, so they don't recognize some of the signs. Some of them aren't even willing to admit that they don't know those things, and they don't refer patients — and referral to major medical centers is a critically important issue. Another issue is that in some societies, healthcare is not sufficient for a large portion of the population, so that known diseases can not be diagnosed or can not be eliminated because patients can not go to a tertiary care center and get the specialized care and diagnostic pursuits that are needed. So I think there are social and academic, medical institutional factors. Some of them are related to money and some are related to people not actually doing their jobs, by not learning enough or referring when they should.

“One major issue is that physicians and healthcare workers are not familiar with a lot of the rare diseases, so they don't recognize some of the signs. Some of them aren't even willing to admit that they don't know those things, and they don't refer patients.”

Sean Sanders:

Avril, from your European perspective, is there a difference in the education of doctors in Europe or around the world that allows them to better detect and diagnose rare diseases, or is this a global problem that is not really country-specific?

Avril Daly:

I think the issue is global. The situation is a challenge across the board for the various reasons that have already been highlighted. The issue with referral that Bill has already brought up is particularly important. The fact that “I don't know what it is. I don't know who to refer to. So I don't do it.” does happen, and it is very sad that it does happen.

At the European level, we have been working for a number of years on the development of European Reference Networks. We have developed, through the European Commission, a sort of a “hub and spoke” model. We have a hub with 24 different disease areas — say, for example, an expertise center on liver, or an expertise center on the heart, or the skin, or in my case, the eye, etcetera. Each expertise center has a hub somewhere in a European healthcare setting, in a hospital setting. Each hub has a spoke system. To become a member of a European Reference Network,

centers around Europe must fit and reach specific criteria set by the European Commission, in collaboration with member states and experts in those states in specific areas.

The European Reference Network allows for better diagnostics among other things. It is currently five years in operation, it is very much still in its infancy. The ambition is to use databases as centralized systems, so that if somebody walks into a hospital in Ghent, for example, in Belgium, with a very unusual condition, that clinician, in that center, is linked in to a European center, and can connect through that EPMS system and say “This is the expert in this area, and this is somebody that I can refer to.” It is a case of finding ways where the expertise, and not necessarily the patient, can travel, so we can speed up the diagnostic journey.

These European Reference Networks are also very important for the development of care pathways. We didn’t know as much in the space of rare diseases as we do now, therefore, there didn’t used to be a care pathway for specific conditions. Now, we can develop them through these networks.

Also, we can learn how to better share data. This is incredibly important. In Europe, we are working on the European Health Data Space. It is essentially a way in which we can start to look at how we generate data, how we curate that data, and how we utilize that data appropriately, so that we can address a lot of the challenges that are faced. Of course, that will also form part of our European Reference Networks. It is a sort of a one-stop shop.

Ultimately, we also hope that this will help us to drive innovation. The more we learn about disease, the more we can research those conditions. It is a very important step forward from a European perspective, based very much on American models as well. We are very hopeful that the technologies that are currently being developed, and the ability for the doctors and the researchers to communicate better through these networks, will lead to better diagnostic options and a more speedy diagnosis for patients. From an education perspective, which was your question, these networks are the way in which we can provide that education to our doctors.

“The technologies that are currently being developed, and the ability for the doctors and the researchers to communicate better through these networks, will lead to better diagnostic options and a more speedy diagnosis for patients.”

William A. Gahl:

I agree, I think the European Reference Networks are spectacular. I would like to point out that a few years ago there was a proposal to have a European Reference Network for rare and undiagnosed diseases, and they decided not to do it. The problem is that not all patients fit into the specialty that is covered by one of the ERNs. I still think it is a good idea to have a more centralized system.

The second point I would make is that there is no specialty in medicine for rare and undiagnosed diseases. There is a person in Hungary, named Bela Melegh, who is working on developing a certification within Europe that is not binding or it doesn’t get you in, but that offers the person who has that certification enough

prestige, which will enable the person to be respected enough by universities to take care of patients who don’t have a diagnosis yet, or who have a rare disease. I think that it would be a great step forward too.

Avril Daly:

I agree. I remember all of this happening at the time, and it is what we have been informed as patients, and we are working with these ERNs and with the Commission on all of this. It is an evolving situation. The hope is that some of the networks can work together as well. For example, in the eye and endocrine diseases, there are a lot of different crossovers, and hopefully we will find a way to be able to address these issues and evolve. One of our biggest issues is the fact that we are dealing with parents all the time, whose children just don’t have a diagnosis, can not get access to a diagnosis, and nobody knows where to send them. We hope that this is a step forward. It is, as I said, five years in practice right now, but still very much in its infancy. We hope that it will get the support from European Commission that it really does deserve, in order to be able to develop in the way that you have outlined so eloquently.

Sean Sanders:

Charlene, I saw you nodding your head to a number of the comments. I just wanted to come to you to see if you had any thoughts that you would like to share.

Charlene Son Rigby:

I am excited to learn about these reference networks. Just from a rare epilepsy standpoint for instance, when we got my daughter’s diagnosis, we were at a major academic center in San Francisco, and we had a very dedicated neurologist and a dedicated geneticist. The first thing that they told us was that they had never diagnosed a child with STXBP1. There wasn’t even a next step. We need to be able to give patients and their families a next step. Standards of care and being able to leverage experts in a remote way — because there are never going to be enough experts for each of those individual rare disorders — are hugely important. I am very concerned about the multi-system issues that Bill pointed out because, for instance, it applies to a lot of neurodevelopmental epilepsies: the child might present first with seizures, but also with behavior and autism issues, or GI issues. So their point of entry into the healthcare system might be very different, while they still need to find the way to that particular expert or standard of care. That is the challenge before us: to get them through that initial triage period as quickly as possible.

Cristina Casanova Might:

One of the interesting things that Avril, Charlene, and Bill have touched upon is provider education. That is one of the culture shifts that I think needs to occur, or needs to be instilled a lot earlier as we train doctors, but also nurses and geneticists, and others who are in the space. I think the willingness to collaborate right now has not been historically as ingrained as it needs to be, and technology can only do so much. The technology that we have is simply phenomenal, and a lot of what we are capable and able to do now is fantastic. For me, the bottleneck seems to be, in

many cases, collaboration. That is why, in the United States, the Undiagnosed Diseases Network has been so truly successful and phenomenal, because it is a group that has really focused on collaboration and innovation. More broadly, it just needs to happen, and it needs to start happening sooner, and not just within very deep specialties. It needs to start in the pediatrician's office, having the paediatrician willing to admit that she or he does not know.

“One of the interesting things [...] is provider education. That is one of the culture shifts that I think needs to occur, or needs to be instilled a lot earlier as we train doctors, but also nurses and geneticists, and others who are in the space.”

William A. Gahl:

I think sharing and collaboration are greater now than they were 10 years ago, and then it was greater than it was 20 years ago. Part of it is technology, but part of it is an understanding that as physicians and researchers, we don't know everything, and we can make a lot more progress working together. One of the things that was mentioned previously had to do with finding researchers to study particular disorders, especially new disorders. Once they find out that there is a human being who may have a disorder that is new, and that is within their wheelhouse of scientific research, they are usually overjoyed. Part of it is because there is a financial incentive: they can probably get a grant more easily if there is a human disease associated with it. But remember, researchers are intrinsically curious and want to find out new things. I think if we had more resources, one of the things that I would spend more resources on is having someone look up the researchers who study each of the individual candidate genes that are part of the evaluation of our undiagnosed patients, and see if one of those researchers wants to pursue the variant that is found in a gene in one of our patients that doesn't have a diagnosis yet. I think that would be incredibly profitable in a way to leverage the total knowledge of our world.

Sean Sanders:

I would like to move on to talking about what can make a real difference in the detection and diagnosis of rare diseases. Who are the stakeholders? Who needs to be involved? We have talked about a number of different groups already, but I am interested to hear if there are any groups that we haven't talked about. Charlene, I will come to you first. AI is one of the newer areas where computer technicians and programmers, who maybe didn't have anything to do with or didn't know about rare diseases, are now having a huge impact.

Charlene Son Rigby:

Certainly, the players that we think of most are the providers, the medical insurance companies, healthcare access policy makers. But as a technologist, I think that we really can be active stakeholders. There has been a tremendous push in terms of technol-

ogy and development in the area of rare disease, analyzing rare disease and diagnosis. At my previous company, Fabric Genomics, we worked in artificial intelligence development, and we were specifically developing an artificial intelligence algorithm called GEM, which is used to bring together phenotype information and genomic data to accelerate and scale diagnosis. This technology is being used, for instance, at Rady Children's to accelerate diagnosis of newborns in the ICU where truly every minute, every hour, matters for these children. It is interesting that you used the word “stakeholder” because I think that for a lot of folks who have been in the technology industry and may not have a background in biology or in rare disease, thinking of them as a stakeholder — where they really are an active contributor and have a stake in this arena — is very powerful from a motivation standpoint.

Sean Sanders:

Avril, do you see any new groups or groups that we are not talking about that should be involved in this discussion?

Avril Daly:

I agree with Charlene, in relation to bioengineers, engineering, data specialists, IT sand pecialists. This is very important in how we are going to address the issue of diagnosis. We know how exciting AI is and we have seen how exciting it could be for us in this community from a diagnostic perspective. The innovators in that space absolutely have to join the traditional groups such as the patients, the industry representatives, clinicians, nurses, counselors, and scientists. They are the groups that we traditionally think of, but it is very important to include those other communities. We are starting to see that actually, even here, they are becoming more involved in research applications that we are doing. We are starting to see that sort of interest and that understanding of how to engage, and it is great. From our perspective, going back to this idea of education, we are seeing in the patient community that engineers are taking the initiative to reach out to us to ask questions.

What could also be important, in general terms, is to sit down with people living with rare diseases and just talk to them. These guys find solutions sometimes through general conversation, and that is something that should be encouraged and is exciting in this community. We call it the necessity of ingenuity: we can talk to each other, and listen, and experts will hear the needs and maybe understand what the solution could be.

“The innovators in that space absolutely have to join the traditional groups such as the patients, the industry representatives, clinicians, nurses, counselors, and scientists.”

Cristina Casanova Might:

I am going to put my industrial design hat on and say that I really don't see that anybody is not a stakeholder in rare disease. I think everybody is impacted, and what I personally would like to see more of in the space and brought to the table are some

of these other, maybe softer, more human expertises as well, including communications and visualization, because being able to communicate that data is key. All the data in the world is not going to mean anything unless people can parse it and understand what someone is saying. Sometimes one word can mean multiple things to different people. Being able to translate from a patient to a doctor to someone who is in industry is valuable: sometimes the same word means something totally different to all the different stakeholders. So if there is a way to refine those pieces of technology and bring in that communication expertise I think that we can hopefully move the progress on all of these rare diseases a little bit more quickly. It would be to our detriment to ignore the fact that it takes everybody to make something happen for these patients and their families.

William A. Gahl:

I agree that everyone is a stakeholder, but I think that there is one group that is not represented at the table right now, and that is poor people. People in poverty have been abandoned by the social network, and so cannot access an Undiagnosed Diseases Program. In a way, we are all part of a club that is privileged, and our patients are privileged. But there are other places where this is just not true. In the United States, it is certainly true that there is a disparity in the ability to get to rare disease experts and to undiagnosed diseases experts. It is perhaps even more true elsewhere in the world. Poor people are not at the table and they need to be. We need representatives of those populations in other countries and within our own country to sit at the table.

“Poor people are not at the table and they need to be. We need representatives of those populations in other countries and within our own country to sit at the table.”

Cristina Casanova Might:

Absolutely, Bill, that is 100% correct. Advocacy plays such a huge role in whether or not a disease gets researched, whether it gets funded, whether you find partners within pharma or others to develop therapeutics. If you are poor, you are not likely to have the time or the other resources necessary to be able to pursue advocacy to the same degree that others can. We are filling that gap for some, but it needs to be done for everybody and globally.

Sean Sanders:

I would like come back to the advocacy side. Charlene, what is the role of advocacy in driving and directing rare disease research? Cristina has already mentioned some aspects of that, but I am also wondering about the impacts of using the internet, social media and online support groups within the rare disease community.

Charlene Son Rigby:

This is something that I am passionate about. We have talked a little bit about the fact that patients are oftentimes starting and sparking things for research into their particular disorder. It has been a hugely exciting time where we are seeing patient advocates starting foundations, research organizations, companies, assembling advisory boards, scientific advisory boards, defining research roadmaps even if they had no research background, and building registries. Patients have that urgency because every day, and every week that goes by is significant. They can not wait. Oftentimes, patients have to put together at least a basic amount of data to get researchers interested. They can share information about their disorder and spark the interest and excitement for a researcher to take their disease on.

I think that social media has been a game changer. You are now not necessarily limited to your region or your direct contact network, but you are able to reach people around the world and to do it in a very general way. I have seen groups that are, of course, around a specific diagnosis or disorder, but also groups of undiagnosed patients looking for people based on symptoms, and even diagnosed patients aggregating into groups of people with similar symptoms. So it is a completely different way of creating a network worldwide. In fact, I found the co-founders for the foundation that we started for STXBP1 on Facebook! It would probably have taken me 20 years to find them without that tool. Social media also enable communities to activate. So once you have built that community, whether it be on Facebook or on Twitter or on one of these more specific disease social networks, you now have the ability to interact with that community and to count that community. One of the things that I think we are all challenged with is, “How many patients really are in this community?”. Social media give us the ability to start to get to what those numbers look like. It is incomplete, obviously, but at least a start to count those patients, and then activate the community to participate in research, to fundraise ... all of those important things that are important to understand a disorder and start to develop therapies.

Sean Sanders:

Bill, from a clinician’s perspective, what impacts do you see advocacy groups having on the direction of rare disease research and even treatments?

William A. Gahl:

Advocacy groups are incredibly important. For one thing, they tell us what needs to be studied. They tell us about the natural history. They allow us to recruit enough individuals to know what the disease is like. They also advocate outside for researchers. For example, a clinical researcher is unlikely to study a disorder if there is only one or two patients. There needs to be enough patients to get enough information. There is also some political advocacy that occurs, and occasionally financial advocacy and assistance. But I would say that the most important thing is to know the disease, and in order to know the disease, the clinical researcher or physician need to see enough patients with it. Advocacy groups also mean a lot to people who are funding research. For example, if you write a protocol and ask for help from the NIH or from some other foundation, one of the first things they will ask is, “Do you have an advocacy group behind you? Are there enough patients

to study?” So it is critically important to have advocacy groups. And it is also, of course, really important for the patients to have someone to share their stories with and to work together.

Sean Sanders:

One aspect that we haven't really touched on very much is the research side. I am particularly interested in incentivizing pharma and biotech companies to do more research into rare diseases and particularly treatments. Cristina, do you have any thoughts on how to best do this? Is it happening at the moment? Are there some good models for this?

Cristina Casanova Might:

I think that there are currently more models than there were 5 or 10 years ago. Technology has improved, not just in diagnosis, but also in the development of therapies. You don't need large patient cohorts anymore to develop new therapies. New therapies are still coming onboard even for small, N of 1 conditions. You can find companies and non-profits who are willing to do it. It is just a matter of knowing who those people are, connecting the stakeholders and advocacy groups, or at least having these communities form and work together in order to find who those patients are, be able to let people know how to get diagnosed and how to get treated ... to be able to hopefully work together to address policy changes that need to be made nationally, locally, and even within the hospital systems. I know here in the US, for example, not every hospital system can do gene therapy or the delivery of an ASO treatment. So being able to continue to incentivize collaboration, I think, is critical, but so is also the funding of these technologies more broadly. Hopefully, the idea that this is a zero-sum game has gone away, but I think that it is still sometimes present in academia. Technology has been a real game changer in that it is not a limited pie: the pie keeps growing. I think that there is room for everybody and if we are collaborating, we can optimize those resources and use them more wisely. There are definitely ways to incentivize biotech and other industries to develop treatments because they are already doing it. It is just a matter of getting to those people and connecting the right players. At least it is the case here, I would be interested to hear what Avril says on how it is going in Europe.

Avril Daly:

Certainly, it is exactly what I would say myself. It is kind of going back to the important conversation we had earlier around social media and engagement to spark research and enable treatment development.

I think it is very important for patient organizations, when they come together to support research, to understand what that journey is, how long that journey can be, and the various obstacles that will be faced on that journey, all the way through from conceiving a research idea because of an unmet need, to actually understanding how to build a register, what data needs to be collected, and patient-reported outcome measures, endpoints, clinical trial design ... All of these issues need to be understood by patients because they are in this space for a reason: because they want to find treatments for unmet needs. Patients need to work together with the industry, and conversations between pa-

tients and the industry are now taking place more than they used to. They are talking about these issues: how they can develop infrastructures to address them and how they can work on them together. Patients and industry are communicating at a very early stage about molecule development and then discussing, “Actually this is what has benefited us, this is what you need to consider”.

Also, as previously mentioned, there is innovation coming out of patient organizations because you have people like Charlene and Cristina who have experience and understanding of the space and how they can make it better, and we must also consider, support and include other people who don't have this experience.

But also, innovation is coming out of patient groups. Registers are coming out of patient groups that are being developed and invested in. We should start asking more questions such as: Where do these registers go? How are they sustained? Who is going to stay in those registers? Who is going to develop them? Is the national health care service provider going to do that? Is industry going to do that?

More and more communication needs to take place, and I think we have learned from the whole COVID experience that we, as a community, can use platforms like this to communicate regularly and readily to address these issues around which, perhaps, we wouldn't have been able to come together to discuss before. So we have huge opportunities now to really not lose the momentum, move forward, and understand that we are all stakeholders in this field. We are all doing this for different reasons, but ultimately, we want to see benefit to the patient and we have to, in order to achieve that, really engage together from the outset and that includes industry. And they are definitely doing that, in my experience.

“Patients need to work together with the industry, and conversations between patients and the industry are now taking place more than they used to.”

William A. Gahl:

There are a couple of concrete incentives for industry that have occurred. One of them is the Orphan Drug Bill of 1983 in the United States, which allowed for exclusivity if there were approval for rare disease or for an orphan drug. Another thing is that some of the fees are waived for the new drug approvals, and that amounts to a huge amount of money, sometimes in the \$100 million range.

Another point is that if a pharmaceutical company has moved forward a drug or a treatment for a rare disease, it can try to sell it based on the fact that it might also treat a common disease. That is maybe just about the greatest incentive for drug companies, in my experience. So drug companies get the foot in the door with the rare disease, and then they can test a large number of individuals for the more common disease and extend the indication. That is a big deal in my opinion.

Sean Sanders:

We are running out of time, but I wanted to quickly touch on a couple of other things that were brought up. Avril, some-

thing that occurs to me is that you have all of these countries or different groups trying to come up with new solutions. Is there a danger that there is going to be splintering if there is not sufficient communication? If so, how do we bring together all of these different countries and different groups who are developing amazing new technologies, databases, innovating, so that we don't reinvent the wheel multiple times?

Avril Daly:

I would say that there is splintering. For example, in my own space, in the inherited retinal degeneration space, I was diagnosed when I was 23 with retinitis pigmentosa. Now, I know that gene, but there are 300 different gene types. There are different genes that are very progressed along the research journey towards therapy and that is very exciting. So there is splintering happening in a lot of disease areas currently, and that is fine. People want to support the condition that they or their child are affected by. But there are some fundamental things that we can work together on, and that is what we have been discussing here today. We can look at the overarching policy issues. Those policy issues are related to all rare diseases, for example, the issue of diagnosis, the access to a diagnosis, access to a genetic diagnosis, what happens to that piece of information, how we use the data ... All these issues are general issues that we can work together on.

In specific disease areas, say, for example, in metabolic disorders, or endocrine disorders, or liver disorders, they may be different diseases, but there may be overarching areas that groups can coalesce and work together on. In our area, we work together on issues concerning registers, research, infrastructure around research, but also on regulatory issues. How do we deal with the issues that are emerging with new therapies, etcetera? It is very important that we educate together: not just the patients, but also the researchers and the clinicians as well, because they are new to all of us. I don't agree with the reasoning "I have this very specific gene, so I don't need to work with that other group". You do. If you really are serious about getting a therapy from an unmet need to the delivery to your child, you have to work with all of these groups because they are the same issues. That is why we need to work more universally, more globally. Coming back to the very first point that we made about the classifications of these diseases, if we are starting at a base where we have such diversity, we are going to be challenged at every point. So these conversations need to happen, they have to be global, and we have to work together on the overarching issues.

Charlene Son Rigby:

Just to add to that, each individual disorder obviously needs very deep research, but at a fundamental level, we do need to come together. Technology is not going to solve everything. It is clearly critical, and I think that we are at an exciting time. This is not specific to rare disease, but with cloud technology, data lakes, AI that we were talking about before, we really have this ability to bring together data. But we need to address issues like consent, being able to harmonize governance. How do you bring data across national borders? Say there is only 10 patients in one country, 15 patients in another, and one patient in a third country: we need to be able to bring that data together and enable researchers to mine it. So all of these more high-level issues need to be addressed across rare diseases so that we can further the treatments we need to develop for our communities.

Sean Sanders:

Finally, Cristina, what should the general public know so that they can be better advocates for rare diseases? Is there a message you would like to send to them that can bring them onboard and help them push some of these policies and ideas forward?

Cristina Casanova Might:

Rare is common. Everybody is affected. It will affect you. There is someone you know, either you yourself, a loved one, colleague, family member, you name it, who is dealing with a rare disease in this very moment. We will all be better off if we work together to solve these conditions. Society as a whole will benefit, but also you yourself will benefit. We all benefit when we create a better, happier, healthier, more just world, and I think that is what everybody on this panel has been all about. So I am very happy to be a part of this, and thanks for having us.

Sean Sanders:

Thank you once again to our fantastic panel, and to Fondation Ipsen for enabling this conversation through their kind sponsorship. Goodbye everyone.

Combating the fragmentation of data and disciplines: Innovation hubs to address rare diseases

Data show that collaborative endeavors are more impactful in biomedical science than are solo operatives. This issue is particularly relevant to the rare disease research community because it is formed as a conglomerate of labs or centers—each with their own cluster of scientists, clinicians, and patients—studying different, uncommon diseases.

Although each rare disease may have only a few patients, there are many commonalities. Common needs include access to genetic testing, ethically regulated data access, psychological counseling, advocacy tools, and the need for fundraising to race for cures. Techniques, technologies, or treatments applicable to one disease might be transferable to others. Collaborative networks need to be fostered to meet the shared needs of the 350 million-plus patients affected.

Innovation hubs could provide a viable option to leverage common goals and opportunities, providing shared protocols for handling phenotypic, clinical, and genetic data, while also prioritizing and amplifying the voices of patients. They could bring together the best international policy structures to streamline efficient and effective medical and scientific advances in rare disease detection, diagnosis, and treatment. This webinar brings together key opinion leaders to discuss the current and future needs of patients, and how innovators, doctors, scientists, drugmakers, and policymakers can work efficiently together to deliver solutions to the millions of diagnosed and undiagnosed patients in need.

Panelists



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ERGOMED PLC,
Raleigh, NC



Anna Lehman, M.D.
University of British Columbia and Vancouver
General Hospital, Vancouver, Canada



Vinodh Narayanan, M.D.
TGen,
Phoenix, AZ



Marshall Summar, M.D.
Children's National Hospital,
Washington, DC



Sean Sanders, Ph.D.
Science/AAAS, Washington, DC
Moderator

The Conversation

Sean Sanders:

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

Marshall Summar:

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

Zizi Imatorbhebhe:

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

Anna Lehman:

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

Vinodh Narayanan:

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

Sean Sanders:

Marshall has alerted me to the fact that centers of excellence and innovation hubs are not always the same. Marshall, could you explain some of the differences?

Marshall Summar:

Admittedly, there is a bit of semantics to it. In rare diseases, a center of excellence is based around clinical capacity. In other words, Anna's program in Vancouver has a deep capacity to do

a lot of things for patients: you would expect the ability to care for kids, adults, having all the secondary specialties, all the things you would need to care for a patient. An innovation center doesn't necessarily have the clinical chops, but is a place where they are focused on the research, developing new products, new strategies, new treatment protocols for patients. While the two can overlap, they can actually be quite separate entities.

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

Sean Sanders:

Zizi, could you talk a little bit about what do you do at ERGOMED and how you fit in with those definitions?

Zizi Imatorbhebhe:

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

Sean Sanders:

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

Vinodh Narayanan:

I think TGen has a unique situation, because it is not a major medical center: we are not a big university like the University of Washington, the University of British Columbia, or even a big

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

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

Sean Sanders:

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

Anna Lehman:

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

teresting findings for patients, but they lack the time and capacity to create new protocols de novo and to ship things off from their desk.

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

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

Vinodh Narayanan:

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

Zizi Imatorbhebhe:

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

Marshall Summar:

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

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

Sean Sanders:

Anna, what do you see as the really critical issues that innovation hubs can address?

Anna Lehman:

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

Marshall Summar:

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

Anna Lehman:

That is a very good question. We are trying to integrate tools that try to make it easy for the clinicians to input phenotypic informa-

tion. Characterizing phenotype is not a problem - we have excellent clinicians in these centers of excellence. The problem is: how can we extract the records into a portable format in a time-efficient way? We are hoping that there are software solutions to make that happen, so that we are not just having high level HBO terms that are not helpful for a more granular analysis. That is another challenge.

Vinodh Narayanan:

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

Zizi Imatorbhebhe:

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

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

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

“From the industry's point of view, we make sure that we can find these patients [...] and we make sure that we can find the physicians that have the right experience. We then marry them together so that the patients can get into these clinical trials, to hopefully bring these ready drugs to market quicker.”

Marshall Summar:

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

Zizi Imatorbhebhe:

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

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

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

Vinodh Narayanan:

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

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

Marshall Summar:

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

Sean Sanders:

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

Anna Lehman:

I just wanted to build on what Zizi was talking about with the need for the real-world evidence. We can leverage our centers of excellence by having a better ability to track how new treatments are impacting patients and our healthcare system. We have a major issue in how to make our healthcare system sustainable with what is happening right now: an explosion of fantastic new treatments coming out for rare diseases that are tremendously expensive. These are being shown to be safe and efficacious, and are therefore getting marketing approvals through FDA and Health Canada. Our public insurance program has then to decide about coverage and coverage for whom. The data that was

sufficient to show safety and efficacy is not always sufficient to show cost effectiveness to the degree that is really needed, as well as how total healthcare system utilization is being impacted. So again, I think the centers of excellence, by more robustly collecting information that is then being pooled from all the centers of excellence, are also going to help us with those really tough economic issues that are facing rare diseases, and increasingly so in the next five years.

"The centers of excellence, by more robustly collecting information that is then being pooled from all the centers of excellence, are also going to help us with [the] really tough economic issues that are facing rare diseases, and increasingly so in the next five years."

Marshall Summar:

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

Sean Sanders:

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

Marshall Summar:

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

“If you are working in a rare disease and you are not working with a patient advocacy group, you are missing the richness of data, but also on the people that will encourage you to keep going and the people that will bring patients together for either studies or treatment protocols among other things.”

Zizi Imatorbhebhe:

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

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

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

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

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

Marshall Summar:

I think, as you said, patient advocacy groups and payers make up a whole community that has to get involved with these. It is interesting to watch how the FDA responds. They have become very flexible around rare disease. As they have met with patient and family groups, they sometimes realize the urgency. So when we

are looking at innovation and their engagement with the approval agencies, it has been quite productive in a number of studies that I have seen. I am curious to ask my fellow panelists, since we are talking about incorporating things like whole genome sequence, a lot of next generation data, phenotype... How do you see the role of machine learning advancing in the field of rare disease? There is a lot of buzz around it. It is very popular right now, but how do you see it playing out in the field of rare disease?

Vinodh Narayanan:

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

Zizi Imatorbhebhe:

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

“We have seen AI used especially with facial phenotypical recognition in this space. Another way that we have seen AI used is to help speed up the diagnosis.”

Anna Lehman:

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

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

Marshall Summar:

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

Sean Sanders:

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

Marshall Summar:

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

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

Anna Lehman:

Because of the pandemic, our hospital launched a great Telehealth platform. We can now see patients who live remotely more often. Depending on what the patient's situation is, we might alternate between telehealth and flying down to Vancouver. For other patients, we might do all their appointments with us through Telehealth, and partner with a local physician to do a targeted physical exam that we send them as a sort of a "fill in the blank sheet". That has worked out well for other patients. It has been the one silver lining out of the pandemic that has transformed

families' lives. It is so expensive to travel and to take time off work. I am really happy about that. Back to the first point, I am really looking forward to more neurologists, cardiologists, pediatricians, being able to order this genomic diagnostic sequencing to get faster diagnosis for patients as well. That can happen more locally as well.

Marshall Summar:

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

Vinodh Narayanan:

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

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

Marshall Summar:

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

Zizi Imatorbhebhe:

I am sure that, with the pandemic, everyone has been hearing more about DCTs, decentralized clinical trials. Decentralized trials are essentially just trying to bring the patient closer to the study or to the site as opposed to having the patients coming to the

site. In terms of incorporating technology, you see a lot of various technological aspects in DCT. We have talked about telemedicine. Some of you mentioned that many times, the patients still want to meet face to face. We find that most of these trials are not usually totally virtual, but rather take a hybrid nature, sometimes in person, sometimes from their home.

We also find that the innovation and decentralized trials also help with clinical trial diversity. Obviously, as you are aware of, there is a lack of diversity in our clinical trials. Because a lot of patients that are from underrepresented communities for example, they are not able to access these clinical trials. I think having the innovative technologies, for example, does help with increasing diversity in patient trials, because these patients are now able to access the trials more readily.

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

Sean Sanders:

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

Zizi Imatorbhebhe:

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

Anna Lehman:

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

Vinodh Narayanan:

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

Marshall Summar:

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

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

Sean Sanders:

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

Personalized therapies in rare disease

Even though the total number of patients with rare diseases exceeds 300 million, each rare disease affects only a small number of patients. Consequently, the standard model for developing new medicines is often not profitable enough for pharmaceutical companies to produce therapeutics for the thousands of rare diseases known to exist. In the past, pharmaceuticals designed for common diseases have been repurposed for patients with rare diseases.

However, that is all changing: New drug design methodologies allow us to contemplate designer medicines for very small groups of patients or even individuals. The future holds promise for the rare disease community because modern biotech can build bespoke (customized) therapies. Are we at the dawn of personalized treatments being widely available for individual patients?

This poses a broader question: Just as every person is unique, could all medicines become so too?

Panelists



Viviana Giannuzzi, Pharm.D., Ph.D.
Fondazione Gianni Benzi Onlus,
Bari, Italy



Tiina Urv, Ph.D.
National Institutes of Health,
Bethesda, MD



Genine Winslow, M.Sc.
Chameleon Biosciences,
San Anselmo, CA



Sean Sanders, Ph.D.
Science/AAAS, Washington, DC
Moderator

The Conversation

Sean Sanders:

*Welcome to this third webinar in our 2022 Science and Life series on rare diseases, entitled *Where Hope Knocks: Personalized Therapies in Rare Diseases*.*

Tiina Urv:

My name is Tiina Urv. I work at the National Institutes of Health, the NIH, at the institute called NCATS, the National Center for Advancing Translational Science. I work in the office formerly known as the Office of Rare Disease Research, recently renamed the Division of Rare Disease Research Innovation.

Genine Winslow:

My name is Genine Winslow. I am the founder and CEO of Chameleon Biosciences. At Chameleon, we focus on treating rare diseases, rare genetic diseases. I have married my background in immunology with gene therapy to develop a technology that allows us to treat more patients and address a broader range of different types of diseases.

Viviana Giannuzzi:

My name is Viviana, I am a regulatory and ethical expert in the rare disease field. I coordinated the research department of the Benzi Foundation, a not-for-profit research organization based in Italy. I mainly work as a researcher in European collaborative projects on pediatric and rare diseases and medicine development, like EJP RD, the European Joint Program for Rare Diseases, C4C, and other ones. I am also a rare disease patient, and I am part of a patient association on rare tumors, based in Italy as well.

Sean Sanders:

So jumping right in, standard models for drug development don't work particularly well for rare diseases, and treatments for common diseases are frequently repurposed for rare diseases. These include orphan drugs that don't have a disease but have been developed by pharmaceutical agencies and essentially put on the shelf for potential use later. However, new drug design methods are now enabling the development of more individualized therapies for small groups or even for single patients. What is your definition of precision medicine or personalized medicine? What does it mean to a patient in reality? Viviana, maybe you could start.

Viviana Giannuzzi:

Precision medicine does not have a unique definition. In theory, personalized medicine is a therapeutic strategy tailored to an individual patient: the right person at the right time, based on its gene, lifestyle, and environment. Precision and personalized med-

icines are particularly relevant to rare diseases. We sometimes have one patient in a country or in a region, so precision medicine, personalized medicine, is a unique opportunity for a patient to be treated with the right treatment, or even to be diagnosed. We need a lot of efforts to develop these kinds of medicines, because it still represents, even today, a challenge for research, for companies, for institutions and medicines agency evaluators.

“In theory, personalized medicine is a therapeutic strategy tailored to an individual patient: the right person at the right time, based on its gene, lifestyle, and environment.”

Genine Winslow:

I work more on precision rather than individualized medicines. I work on gene therapy, and specifically gene replacement therapy. That means that we can treat a genetic disease that is generally caused by a defect in the patient's own gene by supplying that patient with a correct version of the gene. This field is relatively new, although we, investigators and clinicians, have been making great strides. We focus exclusively on rare diseases for several reasons. It is a way to help people that have no hope, that have absolutely nothing else. It is also a way for us to get input from regulators, the FDA and European regulators, about our technologies in an accelerated manner. I think it is a very important space to be working in. It is where we can make the most progress with novel and cutting edge technologies. This is why, for most of my career, I have been working exclusively in the rare disease space. From a drug development perspective - because that is what we do, we are developing genetic medicines - the challenge is to get specific showing clinical efficacy. This is a challenge in the rare disease space in general. Some of these diseases can take years to manifest. They can also take a year or two or more to show improvement in the condition. Our drug development models don't have a law assessing whether a drug is working in clinical trials. Our current system doesn't allow for slow, steady, continued progress in improving a patient's health. Particularly in rare diseases, regulators can work with us to develop new models, new ways to analyze clinical data, so that we can start to bring treatments for patients, even when the total number of patients with a particular type of disease is very small.

Sean Sanders:

Thank you, Genine. You touched on several topics that I am keen to come back to. But first, Tiina, what is your take on precision medicine? Also, could you tell the audience what the difference between precision and personalized or individualized medicine is?

Tiina Urv:

When I think of precision medicine, I think of the following: if you are treating a disease, you are looking at a target and you want to get right at the target. When you are looking at a disease that

has a large number of patients, you have a large cohort of people that you can do the clinical trial with, and you try to find the best drug for the most people. Unfortunately, with rare diseases, you don't have that big number of people, and you also get the people for whom that drug doesn't work. You aren't finding that exact hit for that individual. That is what I think precision medicine is: you are looking at something that hits a specific target. Personalized medicine is more linked to an individual, for example, at the N-of-1 trials where you only have one patient.

I think it is important that we are using personalized and precision medicine, because in a lot of the rare diseases, you may do a clinical trial and have a lot of people who respond, however, you may have a group of people for whom it doesn't work. You really need to go back and look at why it is not working for those people and why is it working for some other people. It is more "personalized" when you are looking at those individuals and it is more "precision" when you are targeting something specific rather than a symptom. You are targeting where the disease comes from, how it starts and what causes it, as opposed to a symptom such as pain or fatigue.

Sean Sanders:

Personalized medicine also looks at the individual's genetic background and other factors... You don't necessarily do that in precision medicine.

Tiina Urv:

Exactly. You are really looking at the individual and what their genotype or their gene makeup is. That helps you understand why they may be responding while somebody else doesn't. You look at the differences between the people.

Sean Sanders:

Tiina, you mentioned N-of-1 clinical trials. Could you please define what they are?

Tiina Urv:

Generally, when you do a clinical trial, you have a large number of people and you have a comparison group. One person gets the drug, one person doesn't get the drug. In an N-of-1 trial, you basically have one person. They get the drug, then, they may have a period where they are not getting the drug, they may then get the drug again... There are various models, but they are their own comparator group. That is the simplest way of putting it.

Genine Winslow:

Our clinical trial sizes are not necessarily an N-of-1, they are more an N-of-15, which is still a very small number. Typically, for a standard drug, you would have hundreds of patients enrolled in your first clinical trial. The way that we assess whether a drug is working is based on statistical relevance with those large numbers of people, which is much easier to show when you have access to hundreds of people. The challenge is: how do you show meaningful significance when you don't have the luxury of hundreds of people? This is a road that is being paved as we speak for gene

therapies. It is an evolving conversation. The overriding goal of regulators is to ensure that drugs work and are safe. The challenge is: how do we do that with N-of-1 or N-of-15? You hit on something that is very important when you are working with these very small patient populations: the patients are their own comparators. N means the number of patients in a clinical trial of 10 or 15. Sometimes, we do running studies, where we monitor the patients and measure, looking at the test we use, to determine whether or not the drug is working. We call it clinical N points. We show what these N points are in each individual patient before they have been given the drug and compare it to what is happening after.

That is one way to show that these drugs are safe and effective even with really low numbers of patients. My particular field with gene therapy has a twist, because the current technology is a “first generation virgin”: it can only be given to a patient once. This is because of the immune response to the drugs: each patient will respond differently to that drug. Our technology finds a way to deal with the immune response to the drug to reduce it, so that we no longer are limited to just one dose. We can give more than one, and we can monitor the patients, and give them as much as they need to be sure that the gene we are replacing is working at a functional therapeutic level.

“The way that we assess whether a drug is working is based on statistical relevance with those large numbers of people, which is much easier to show when you have access to hundreds of people. The challenge is: how do you show meaningful significance when you don’t have the luxury of hundreds of people? This is a road that is being paved as we speak for gene therapies.”

Viviana Giannuzzi:

I think that we touched upon two key topics strictly linked to innovation. The first topic is the way we develop a medicine, gene therapies, through personalized medicine. In this context, we need the full acceptance of regulators for patients to have this opportunity on the market. We need to demonstrate to regulators that our product, even if it is innovative, and even if it has been tested on a relatively small number of patients, is efficacious, safe and qualitative.

Secondly, we have new innovative research methodologies, such as the N-of-1 clinical trial design. We also have a lot of other new trials and trial designs that are alternative to the classic randomized clinical trials. It needs a lot of patience, which is difficult or even impossible to have in the field of rare diseases. Even so, we need the approval from regulators, from the regulatory medicine agency, that the new methodology is enough, and that it provides data that ensures that the patient will have a good product.

We really need to implement everything that is new with regards to the way to develop medicines, but also the way to test medicines. To prove that our product is okay for patients, it should be accepted by our local agency, but also fully accepted by all agencies and institutions around the world.

Tiina Urv:

Viviana brought up a really good point which is that there are a lot of other technologies available. One of the things we talk about a lot at NCATS and the NIH is that, there are over 7000 rare diseases: it would take forever to do personalized and precision medicine for every individual with a rare disease. Therefore, they are working on technologies, or different models, such as platform models, where you look at patients that have commonalities in the disease, and you can do either basket trials or umbrella trials. Basket trials are trials where you have one treatment and a lot of different people with similarities, and you observe who it works best for. So you don’t have to do an individual trial for each one of those people, but you have a group of people for whom you think that the drug or treatment has a good chance of working. You try it on all of them to see who it works best on. Another one is umbrella trials. You can think of umbrella trials as trials where you have one patient that you are bombarding with rain drops: you try a lot of different treatments on that one individual to see if it works. To work in the rare disease space, we really need to think out of the box of how traditional clinical trials have been done.

Sean Sanders:

It seems like the standard ways of doing things are not really working for rare diseases. We need to find innovative ways to do things, but we also need to push the regulators to catch up with the research and new methodologies... It seems to be a stumbling block, because regulations take a while to change, they are sometimes slow moving. But it is fantastic that there are people out there in the rare disease space that are doing this. I believe this area of rare diseases is going to push medicine forward for everybody.

Tiina Urv:

I think they are using some of these ideas in the cancer research, and that really helps the rare disease people to say, “Well, we have a precedent in cancer, why can’t we do it with our rare diseases? It’s very similar.”

Sean Sanders:

Next, I wanted to talk a little bit about genome sequencing and one of the techniques that is used. I know that some do Exome sequencing, some do whole genome sequencing, there are cost issues involved... Genuine, broadly, how widespread is genome sequencing? What type of methodologies are available? How affordable is it? How often is it helpful?

Genine Winslow:

Genome sequencing is now very widespread. When I say genome sequencing, I am not referring to sequencing the entire genome of something. I am talking about sequencing the part of interest, the part that you are working with. I have been in this field for a long time. 35 years ago, I used to do DNA sequencing by hand. We now have machines that do everything: all the chemistries, the reactions... everything is completely different now. Genome

sequencing is like a work horse that supports the development of rare disease drugs, anywhere from cancer to rare genetic diseases like those that I work on.

We have used genome sequencing to figure out why one patient, for example, will respond to a cancer drug, and why another patient with the same type of tumor won't. We have used genome sequencing to dive more deeply into different types of diseases, and try to correlate on a DNA level, how to help particular patients respond better to a drug or a type of drug. Genome sequencing used to be much more expensive. Remember when they celebrated sequencing the entire human genome? It has come so far, even since then, that it is relatively inexpensive. We can sequence very large amounts of DNA in a fraction of the time that we used to be able to. It has changed quite a bit and for the better, and it has become a very common tool that we can use to better understand a patient's particular disease, and the reason why they might be responding better than another or worse than another patient in the same clinical trial.

Sean Sanders:

Genine talked about sequencing specific regions of the genome, so you are not trying to sequence an entire genome, nor the exome which is the parts of the genome that are translated into proteins. Viviana, how do you know which part of the genome to look at to find that answer?

Viviana Giannuzzi:

There is still great variability in this field. More and more countries are implementing genome sequencing, which is more and more specific to a disease or a gene. Prenatal and newborn screening are also specific tests to only a part of the genome. My point is that, even if an increasing number of countries are implementing genome sequencing, in most of these countries, these new technologies are not yet integrated into the routine clinical practice. So, the only way that patients can access genome sequencing in this region, both for treatment and for diagnostic, is to participate in research activities. This is also the only option to get a diagnosis for unsolved cases. This is true, even though, as Genine said, the cost has dramatically reduced over the years. The cost also varies greatly from one country to another. As far as I know, in the US, a genome test costs maybe \$1000. In Europe however, it has been recently demonstrated that the cost is four times higher than that in the US. To summarize, genome sequencing is a great opportunity for diagnosis and treatment, but it comes with great variability across countries.

“Even if an increasing number of countries are implementing genome sequencing, in most of these countries, these new technologies are not yet integrated into the routine clinical practice. So, the only way that patients can access genome sequencing in this region, both for treatment and for diagnostic, is to participate in research activities. This is also the only option to get a diagnosis for unsolved cases.”

Sean Sanders:

As Viviana mentioned, it is often difficult to get a diagnosis for a rare disease, for example, if it has not been picked up by neonatal screening, if it is not a disease that has been seen before, or if it is extremely rare. We often use the term diagnostic odyssey, where the patient, together with their family, launches into the odyssey of trying to find out what the issue is. I know that there are huge difficulties with the diagnostic odyssey: some doctors, for example, will tell patients that it is not a real disease and that they are imagining it. Tiina, could you talk about the diagnostic odyssey, and go a little bit further to talk about the potential treatment odyssey?

Tiina Urv:

I like the term “treatment odyssey” as well. The diagnostic odyssey is something that families go through. I am not a patient or a family with a rare disease, but I spend a lot of time talking to the families and to patients with rare diseases and hearing their stories. What you hear repeatedly is that they just want to know what is causing it. The first thing they want to know is “What is wrong with my child?” or “What is wrong with me?” They often say that once they find out, it is a big relief. However, it can take between three and eight years, with the average of five years, to get a diagnosis. In that time, they are usually seen by at least seven different doctors. The current model is to go to your primary care physician. If they can't figure it out, they spend a little time trying to diagnose you. If that doesn't work out, they send you to the next person, and if that doesn't work out, they send you to the next specialist. We need a centralized place where, if you can't be diagnosed in X amount of time, you should be sent to a broader team of people that look at you from multiple directions – for example, neurological or digestive – to find out the different reasons why you could be having these problems.

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The patients are just first looking for an answer. A lot of times you will hear the family say, “Okay, at least I have a name for it now, I know that I am not making it up, or the doctor is not ignoring me anymore.” Once you get a name for your disease, you then go on the treatment journey - and there are no guarantees. Family groups are often participating in patient advocacy and raising money for treatments. It can be very frustrating because they are raising money for treatments that aren't going to help their own child, but that will be helping a child maybe five or ten years down the line.

Viviana mentioned newborn screening: we have had a lot of discussions about doing whole genome sequencing or sequencing

in general at an earlier time, to pick up some of these disorders to find targeted treatments or at least put them into a pool where they could be found for targeted treatments to occur. Unless you are living in Boston, San Francisco, New York, right next to a research hospital, the chances of you finding the right clinician who is doing research on that very specific rare disease are not very good. There is a problem with equity in where you live, where you are at, the kind of insurance you may have, in even finding those treatments. There are a lot of things in the pipeline that need to be addressed before we can get a smooth route of treatment for the patients.

Sean Sanders:

We also spoke in our previous webinar about centers of excellence, which are one possible solution, as well as the rising role of telemedicine, so that people in remote locations can visit these centers of excellence remotely.

Tiina Urv:

That is great. When you do sequencing, you may find variants in genes, however, you don't necessarily have an answer for it. You might go to a center of excellence, but they may not know what to do with it. Some researcher somewhere else may have the information. Importantly, we need to have more centralized information and communication across the US and the world in general, to match variants, patients and treatments, because there might be a treatment somewhere that doesn't yet have the right patient. Doing that matchmaking would be really important.

Viviana Giannuzzi:

I just had a few comments about the involvement of families and children. When we have a genetic or inherited disease, the involvement of families is much stronger. We need to collect data, the medical history, not only from the patient model, but also from the family that might be involved as well. The diagnosis for children is even more difficult. If we have a genetic diagnosis, we have our panel and our test telling us what the disease is. However, if you would like to have the clinical diagnosis in the rare disease field, then we must rely on the capability of children, even the youngest ones', to express their pain, discomfort, their feelings, and so on. These elements are even more crucial to develop a diagnosis for them. Also, for children, we have not only the methodological issues that I mentioned, but also the ethical issues. We must implement genetic counseling and give particular attention to the involvement of families when dealing with children.

Sean Sanders:

Genine, could you please share your thoughts on the treatment odyssey as well? Could you also speak a little bit more about the gene-based treatments that you are looking at at your company, and particularly the viability of these as a broader treatment for rare diseases? You said that things are quite specific at the moment, it is quite a new area. But is there something that you believe will be viable to treat rare diseases more broadly across the world?

Genine Winslow:

Firstly, the treatment or the diagnosis odysseys are issues with rare diseases partly because of the definition of a rare disease. There aren't many people who have them. Physicians aren't used to seeing patients come with these sets of symptoms. That makes it tough. I really like what Tiina said about setting up some sort of guidelines. If you have not figured out a cause within a certain amount of time, you need to start looking into some of these other rare diseases as potential causes.

The other key factor is that, with rare genetic diseases, a lot of times, the most severe diseases affect children and infants predominantly. In those cases, investigators and clinicians believe that treating them as soon as possible is crucial before they have started to accumulate some of the damage that could be done by a given disease in other parts of their body. That is very dependent on newborn screening. Parents of children with rare diseases have been tremendous advocates of getting newborn screening developed and implemented. It is very complex in the United States because each state has a different panel used for newborn screening. You could be in one state and be lucky enough to have caught a disease, because it is on that state's panel, but if you live in another state, it may go undiagnosed potentially for years, as Tiina said.

To do the most good, we need to catch these diseases as soon as possible, and we need to treat the children as soon as possible. Again, we need to increase access to and sharing of information, and to move away from the model where each state has its own testing policy: it should be universal. All children deserve access to the latest genetic testing, because if they are unfortunate enough to have been born with a severe genetic disease, they deserve to know what it is no matter where they live in the country. Right?

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To comment on our particular technology, I explained earlier that we work on gene therapy. We treat diseases that are caused by a defect in a gene. To illustrate, the most common one that almost everybody knows about is hemophilia. Hemophilia is caused by a defect in a gene that makes a clotting factor that is needed to clot blood. People with hemophilia can have a defect in one or two of the genes involved in that clotting process. That was also the first disease, I believe, to be treated with gene therapy. Clinicians and researchers have shown that we can supply the correct version of those clotting factors to patient cells. Those cells start to make the corrected version of the gene, and then the disease symptoms can be reversed. It can work very well. There are two drugs on the market. One is LUXTURN A (<https://luxturna.com/>) which restores sight in a genetic form of blindness that affects children. The other one was developed by a company called AveXis (Novartis Gene Therapies) to treat spinal muscular atrophy. In this case, children who are born with that disease don't live often beyond two years. Using gene therapy, they have been able to provide the correct

version of the gene that causes that disease. Some patients not only survived but have also gone on to grow and thrive.

Our goal at my company is to be able to do this for all children within a clinical trial, not just the ones that it happens to work best for. Gene therapy has been around probably for 30 years, if not a little more. More recently, we are starting to discover why it works very well in some patients and it works less well in some other patients. For gene replacement therapy, we are finding it has to do with the immune response to the drug. The immune response generated by each individual patient can influence how well that drug works for a particular patient. My company has been working on a way to neutralize that immune response so that we optimize the efficacy or how well a drug works for more patients.

“We are starting to discover why [gene therapy] works very well in some patients and it works less well in some other patients. For gene replacement therapy, we are finding it has to do with the immune response to the drug. The immune response generated by each individual patient can influence how well that drug works for a particular patient. My company has been working on a way to neutralize that immune response so that we optimize the efficacy or how well a drug works for more patients.”

The idea that we can't treat all patients with gene therapy again has to do with the immune response, and with the particular way that a lot of gene therapies are done. Gene therapies are done by using a gutted virus that becomes a shuttle to transport a correct version of a gene into patient cells. Investigators have been working on this for long enough that we have got these very safe, modified viruses. We know they are very safe to give to people. However, they are a virus, and our patients' immune systems see it as any other virus. Even if we have gutted it and put a good gene in it, patients' immune systems don't know that it is a good gene and still attack it. The patients who have been exposed to that virus previously will have developed antibodies to it. Those patients can't be treated - or in the past, haven't been able to be treated - with gene therapy. Our technology is overcoming this issue, so that we can safely treat these patients that might have antibodies to the particular shuttle virus we are using. Our research is at its very early stages. So far, it has been done in animals and two different animal models. However, we have been able to show that once we give these animals our drug, the immune response generated is much lower. We have the opportunity to administer multiple doses very safely without risking some of the immune responses that have been problematic and clinically quite dangerous.

Sean Sanders:

Thank you, Genine. It sounds like there is some very exciting work going on both within your company and more broadly in this area, this is great news. Tiina, would you like to add something?

Tiina Urv:

About newborn screening, there is a uniform screening panel that is recommended by the Health and Human Services. To be added to that panel, which most states pick up, the disorder must have some sort of treatment or some sort of effective manner of dealing with it. The challenge is that states add disorders one at a time. But when you have 7000 disorders, it is hard to get a treatment for them. There is also the quandary around the fact that if you did whole genome sequencing on everyone, you would pick up all these super rare diseases that there might not be a treatment for, but you would also know how many people there were with it, or where to find those individuals if a new treatment came up. However, because they don't do whole genome sequencing on everyone, especially with gene targeted therapies, you hit a gap: you need to screen everyone to find them because they are so rare, but you can't screen everyone for them because you don't have treatments for them... But you can't develop a treatment until you find them all.

“About newborn screening, there is a uniform screening panel that is recommended by the Health and Human Services. To be added to that panel, which most states pick up, the disorder must have some sort of treatment or some sort of effective manner of dealing with it. The challenge is that states add disorders one at a time. But when you have 7000 disorders, it is hard to get a treatment for them. [...] You hit a gap: you need to screen everyone to find [rare diseases] because they are so rare, but you can't screen everyone for them because you don't have treatments for them... But you can't develop a treatment until you find them all.”

In the future, I think that there are a lot of things that would have to go into place to do whole genome sequencing for every newborn. We would have to learn how to call variants better, we would need a lot more genetic counselors, we would need people to be able to interpret... If it did happen, we could find answers for a lot of diseases, but there are a lot of things that need to be in place in the pipeline to support that, such as people, jobs, knowledge and sharing and pooling of information. That is a dream world.

Genine Winslow:

Yes, the cost of sequencing has gone way down. But it is not yet accessible to everyone, and at this point, we aren't able to sequence the entire genome for every pediatric patient. It is just not feasible. Even if we could, we wouldn't know what a lot of it meant, and I think that is what Tiina was alluding to. We have identified certain diseases for which we know exactly what is causing them. If it is a genetic disease, it is caused by a change in a particular gene. But two people can have the same change in a particular gene, and one person will have a very severe version of the disease and another person will only have a mild version.

Biology is redundant. For that reason, if we had the entire genome sequence, we wouldn't know what to do with most of it. Therefore, for now, we focus on those that we know, or those parts of the genome that we know or suspect could be causing a disease.

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Viviana Giannuzzi:

The final aim is to have a medicine for a patient. On the one hand, we need to develop treatments as quickly as possible. Advanced therapies, including gene therapies, are sometimes the only opportunity for patients to be cured. Gene therapies and advanced therapies are very often the unique alternative treatment to symptomatic drugs (not curative drugs) or to off-label medicines, which have dramatic consequences. Therefore, we really need to develop advanced therapies, gene therapies for patients as quickly as possible.

On the other hand, again, we need to ensure that patients have safe and quality drugs. This is the role (sometimes the unfortunate role) of the regulators. The problem is that these are the most challenging drugs. We need more expertise. Another important challenge is that we don't work with pills: we work with cells and genes. The challenge is to have equipment and facilities at each level, regional and local, to provide patients with this drug across-the-board.

Sean Sanders:

Tiina, could you please describe to the audience what orphan drugs are? Also, the Orphan Drug Act in the US was passed in 1983, which is almost 40 years ago now. Do you feel it has been successful at driving research into treatments for rare disease?

Tiina Urv:

Orphan drugs don't necessarily need to be in rare diseases. They can be treating neglected diseases. A lot of people could have it, but basically, it is not in the best financial interest of a company to invest money into working in an area where there are only a few people who need it, or, unfortunately, a part of the world that can't afford it. The FDA and the government wanted to push people and give them the incentives to work on those treatments. It has been 40 years, it could have done a lot more, but it also could have done a lot less, it is hard to say. Between 1983 and 2019, 5,099 drugs and biologics received orphan designation. The top three areas that are receiving orphan designations are firstly, oncology cancer. If you are a lump or splitter, it is like each cancer could be rare because if you start looking at individualized medicines, everyone's tumor is a little bit different in how you treat it and how you adjust the drugs for it. For rare diseases, we have

learned a lot from cancer. The second top area receiving orphan designations is neurology. The third one is infectious disease. Also, the one area that has recently started to come up as well is the pediatric diseases. So, we haven't cured all the problems, but it is better than having nothing and no incentives as of this time. In the future, things could be different or modified. We could have worked faster, but there is no guarantee with any ideas that we have did something.

Sean Sanders:

Viviana, do you have any thoughts on this from the European perspective?

Viviana Giannuzzi:

Orphan medicines need specific support from institutions and governments, otherwise they are likely not to be considered or developed by companies and researchers, because the incomes coming from selling them would not compensate the efforts made to develop them. We heard about methodological, economic and ethical issues. Of course, these challenges become even more important when dealing with children. We need ad hoc legislation like in the US, which was pioneer on this. We have other legislation around the world, like the European Orphan Regulation that came into force in 2000, which shares similarities with the American legislation. As Tiina said, the Orphan Drug Act, as well as the European Orphan Regulation, incentivize the development of drugs for rare diseases, but also of other medicines in specific fields where there is no economic interest.

I believe that both the European and the American legislations are successful. We demonstrated in 2017 that they both pushed for a huge number of medicines for rare disease patients in almost all disease areas, as well as for children. However, there are still areas of unmet medical needs: we still have rare diseases with no treatment option, especially for the youngest children or in some specific therapeutic areas. Anyway, the legislation accompanies the development innovation and so on. For example, thanks to the Orphan Drug Act we have in America novel products for rare diseases, and molecularly targeted medicines for children as well. The European Union is trying to do the same because the European Union acknowledges the existence of these areas of highest unmet medical needs. We have therefore incentives for companies as well as research programs to push their development in these specific areas.

Sean Sanders:

So it seems like although a lot of progress has been made, there is still a lot to do in this area.

Tiina Urv:

It is slow progress.

Sean Sanders:

It has been fascinating speaking to all of you. Thank you once again to our fantastic panel.

Bringing Rare Disease care to underserved populations

The plight of patients with rare diseases is a critical, unmet need in global health care. The statistics are frightening: There are over 8,000 rare diseases in the world that affect 350 million people. Only half of rare disease patients ever receive an accurate diagnosis, and one in four patients with a rare disease waits over 4 years for an accurate diagnosis. There is an urgent need to better understand the barriers to shortening this diagnostic odyssey.

Diagnosing and treating rare diseases often necessitates highly specialized medical teams, high-tech diagnostic equipment, and uncommon, expensive therapies. Lack of access to health care for patients with rare diseases is yet another barrier to diagnosis. Consider the fate of a child born with a rare or ultrarare disease in sub-Saharan Africa or an underserved Native American population. Setting aside the social and financial barriers to fulfilling basic needs, it is highly likely that they have negligible access to dedicated rare disease health care teams. However, we are on the brink of new solutions that include accessing specialized care through telemedicine, diagnosis through mail-in specimens, and computer-aided remote phenotyping. This webinar discusses how new systems and technologies can close the chasm that prohibits those with rare diseases living in underserved countries and communities from getting critically needed care.

Panelists



Nakela L. Cook, M.D., M.P.H.
Patient-Centered Outcomes Research Institute
(PCORI), Washington, DC



Linda Goler Blount, M.P.H.
Black Women's Health Imperative,
Atlanta, GA



Jamie Sullivan, M.P.H.
EveryLife Foundation,
Washington, DC



Consuelo Wilkins, M.D., MSCI
Vanderbilt University Medical Center,
Nashville, TN



Sean Sanders, Ph.D.
Science/AAAS, Washington, DC
Moderator

The Conversation

Sean Sanders:

A very warm welcome to this fourth webinar in our 2022 "Science and Life" series on rare diseases, entitled Doing better where it counts: Bringing rare disease care to underserved populations.

Consuelo Wilkins:

I am Consuelo Wilkins. I am the Chief Equity Officer and Senior Associate Dean for health equity at Vanderbilt University Medical Center. I am trained in internal medicine geriatrics, although I now spend most of my time focused on research that emphasizes health equity, which is relevant to today's discussion. I am one of the leaders of a recruitment innovation center that provides guidance and resources around clinical trials, including those for rare diseases.

Linda Goler Blount:

I am Linda Goler Blount, President and CEO of the Black Women's Health Imperative. The Black Women's Health Imperative is the only national non-profit organization focused on Black women's health, and has been for almost 40 years. I am an epidemiologist by training, and we focus on chronic disease prevention, reproductive justice, maternal health, and we have a significant policy shop. I think for the purposes of today's conversation, it is worth mentioning that I am the Chair of the Rare Disease Diversity Coalition (RDDC), which is a coalition of more than 50 pharmaceutical companies, patient advocacy groups and research groups that are focused on trying to understand the drivers of inequities in rare disease, treatment and diagnosis, and to shorten the amount of time from appearance of symptoms to diagnosis to effective treatment, and to improve the research pipeline for rare disease. So, I am happy to be here, and I am looking forward to the conversation.

Nakela Cook:

I am Nakela Cook. I am Executive Director at the Patient-Centered Outcomes Research Institute or PCORI. PCORI (<https://www.pcori.org/>) is a research funding organization that targets the opportunities to provide research funding for studies that will help empower patients and other stakeholders, such as caregivers, clinicians and policy makers, with the information and evidence that is needed to make important health care decisions. We do this by funding comparative clinical effectiveness research or CER, as you may hear me call it today. One of the unique things about PCORI is that our authorizing law emphasizes research for rare diseases. In doing so, it authorizes the establishment of an advisory panel for rare diseases that PCORI taps into to understand the issues important to conversations like today for patients that may be across the country. I am a cardiologist and a health services researcher by background. I have had a long-standing interest in addressing the issues of differential outcomes and health

care access as well as health outcomes amongst individuals that live in different parts of the country, may have differential access by geography, as well as by race, ethnicity, sex and gender, and other issues. This intersection, of thinking about those individuals with rare diseases that may particularly live in underserved communities, is incredibly important to me.

Jamie Sullivan:

I am Jamie Sullivan. I am the Senior Director of Policy at the EveryLife Foundation for Rare Diseases. EveryLife Foundation is a non-profit, patient-focused organization. Our mission is to bring innovation in the diagnostic odyssey, and to improve the development of an access to treatments and diagnostics. I work on our regulatory and legislative initiatives. I really look forward to this panel discussion where I can talk about some of the work we are doing in collaboration with groups like Linda's to help track policies that can not only support innovation in rare diseases, but also help address the underserved, under-resourced populations that we are here to talk about.

Sean Sanders:

I think it would be helpful to start with what we mean by underserved populations, or under-represented populations, particularly those that are dealing with rare diseases. Consuelo, how do you see this population? Where are they and what challenges are they facing?

Consuelo Wilkins:

I think it is important to start with what we are talking about. The term "underserved" itself is a broad term. There are many reasons why populations, or communities, might not be served. I think it is important to contextualize: are we talking about populations not served by the healthcare system, the health delivery system, people not served by research, or people not served by the social and structural support systems that many of the populations we are talking about are really suffering from, being disenfranchised, marginalized minoritized, disinvested? We should try and define specifically which populations we are talking about, otherwise, people might be imagining very different things. When I am talking about these groups, I try not to use the term "underserved" unless I am specifically talking about healthcare utilization or services. I am more frequently talking about groups that have been minoritized due to their race or ethnicity, social circumstances, and other identities.

Sean Sanders:

Thank you, Consuelo. I wanted to add that when I think of underserved populations, I also think of populations in countries that don't have the same access to healthcare that some Western countries have, particularly those living in very rural communities who might be a day of travel away from medical care. Nakela, do you have any other thoughts on the subject?

Nakela Cook:

I would love to give a perspective related to research itself and thinking about the populations that we are talking about when we think about health research. One of the things that we have talked quite a bit about with our advisory panel on rare diseases is that we are often in a situation where those that may have rare diseases have been historically excluded from a lot of the clinical research studies that are undertaken. This is predominantly because either it may not be recognized what symptoms and constellation of symptoms may be presenting with the rare disease, or that such individuals may have other complex health issues that may not have them included in traditional research studies. Therefore, those with rare diseases are historically excluded populations.

"Those with rare diseases are historically excluded populations."

I will also mention that we typically have focused on patients with rare diseases who also live in communities where they may not have access to traditional services, when we talk about utilization of services and underserved. We also recognize that those patients who live with rare diseases may be members of communities that could potentially be defined as not having those access to services, and that could really be considered as "underserved" by definition. So, we broaden the thinking about the access to services and the utilization of services, and, as Consuelo mentioned, about potentially the way in which we think about marginalized populations.

Linda Goler Blount:

Just so people don't get the impression that "underserved" is a passive experience, I would add that in fact, in this country and outside the US, it can be very deliberate. As we look at the effect of 'redlining', which is the systematic disinvestment in certain communities that makes access to quality public schools very difficult, and that keeps people from being able to own homes in neighborhoods that might be closer to academic medical centers, there are many examples of systemic policies that have harmed populations by race, by ethnicity, by income, and obviously by geography. The term "underserved" contains a deliberate attempt to make sure that certain populations don't have access to the kinds of care, research experience and quality outcomes that we are talking about today.

Sean Sanders:

Thank you for making that point, Linda. Jamie, I would like to turn to you to talk broadly about some of the challenges that are faced by rare disease communities, patients and families. Following that, we will talk specifically about how we layer on top of those challenges the challenges that we have just been talking about for minoritized and marginalized communities.

Jamie Sullivan:

Broadly, one of the challenges that we focus on is the diagnostic odyssey and the fact that rare disease patients on average face about a 6.3-year diagnostic odyssey after the initial symptoms have presented and they have sought care. It takes an average of 16.9 different physicians just to get a diagnosis. Keep in mind that these numbers are coming from a study of people that made it through the process, who made it through the diagnostic odyssey. When we know that there are countless numbers of individuals who are still facing that odyssey and who are not connected into the system to even fill out a study, or a survey like this, 6.3 years and 16.9 physicians is perhaps the best-case scenario.

If they are able to obtain a diagnosis, then we see some challenges around access to care. That starts with our systems that aren't generally set up to count, track and help connect rare disease patients to the right resources. One challenge is that only a small fragment of rare diseases has diagnostic codes, and that leads to issues around access to care, prioritization, and connecting the patients into the research opportunities that might be there. It also includes the fact that there are only about 5% of rare diseases that even have treatment options. Another broad challenge faced by rare diseases is the fact that by and large, there are no treatments that have been approved, and so the care that they can access consists of leveraging treatments for symptom mitigation that might be used in other conditions. They also may not even be able to do that because the specialist care is not available for many rare disease patients. We can go into more depth in any one of these areas.

Another challenge is that we have care from specialists that is inaccessible, because there are simply very few specialists in many rare diseases. Generally, people talk about over 7,000 rare diseases, but more and more evidence is coming to light that there are actually over 10,000, and more are identified every day. The patients facing rare disease diagnosis are trying to navigate a system that is not built for that level of specialty care, and certainly not, if they are living in rural areas, not already connected in with the healthcare system. These are just a few of the many challenges that we focus on at EveryLife.

Sean Sanders:

Great, thank you for outlining these challenges, Jamie. Linda and Consuelo, hearing all of these challenges, can you provide us a sense of how these populations that are marginalized, underrepresented and underserved experience the rare disease odyssey? What additional challenges might they have, for example, both when getting access to care and figuring in mistrust of doctors in some communities or language issues in certain other communities..?

Linda Goler Blount:

For patients of color in particular, the diagnostic odyssey, as we call it, can be on average 7 to 12 years. This partly has to do with access, but part of it is also their relationship with their providers. Oftentimes, providers of patients of color don't think about rare diseases. I think that may be true in general: as it is rare, it may not occur to providers. However, through the RDDC, a couple

of examples of patients come to mind. A man was diagnosed with cystic fibrosis at the age of 52 after decades of symptoms. It took that long for providers to finally decide that it might be cystic fibrosis. Another had a rare kidney disease. His doctor told him, "You need to stop eating fried chicken." He is actually a vegan, he had never had fried chicken. There are some things that just never occur to physicians, but we can't make it the patient's responsibility to understand or diagnose him or herself. As you talk about mistrust, we see that once these patients finally got a diagnosis, they can then go back, re-play their experiences and realize how they had been underserved and disrespected along the way.

When we think about what we do to create evidence, of course, the first reason why people of color don't participate in clinical trials is that nobody asks them. It is not because they distrust the system, that is a part of it, but they are just simply left out because providers make assumptions about what they will and will not do and what their adherence would be. Of course, there are a myriad of other barriers around transportation, costs and these sorts of challenges. But what we are hearing through the RDDC is that the providers need to step back and consider for patients of color, for low-income patients, things that they might not ordinarily consider, to give them the opportunity to begin that process and hopefully shorten that time period.

"The first reason why people of color don't participate in clinical trials is that nobody asks them. It is not because they distrust the system, that is a part of it, but they are just simply left out because providers make assumptions about what they will and will not do and what their adherence would be. [...] Providers need to step back and consider, for patients of color, for low-income patients, things that they might not ordinarily consider, to give them the opportunity to begin that process and hopefully shorten that [diagnostic odyssey] time period."

Jamie Sullivan:

To reinforce what Linda was saying, in a recent study that came out, they did universal whole genome screening of babies that were in the NICU and were experiencing some types of symptoms that hadn't been identified. They then went back and looked for those babies that weren't previously recommended for genetic testing, but who should have had genetic testing. They found 67% of the group that had never been recommended for genetic testing were non-White populations. The paper was out of Seattle, it was talking about the fact that there is potentially an inherent bias by clinicians, against thinking about genetic diagnoses in non-White populations. That is a huge barrier for rare disease patients to get an accurate diagnosis.

Consuelo Wilkins:

Perhaps I will frame my points based on Jamie's description of how the system isn't structured and prepared for patients with rare diseases. Imagine that also, for many of these populations that have been disinvested, marginalized and minoritized, the

health delivery systems, the research, clinical research operations, were not designed with these groups in mind. The impact of this is exponential. We have rare diseases on the one hand, and we have a system that was not designed for these individuals on the other hand.

“We have rare diseases on the one hand, and we have a system that was not designed for these individuals on the other hand.”

I would also like to echo Linda’s earlier point about some of this being intentional: we do not want to dismiss or forget that racism, discrimination, and bias built these systems that we are talking about. These are the same systems that historically excluded people from research, excluded people from high-quality healthcare, segregated care... All these things are built into the foundation of healthcare delivery and research. That can’t be forgotten. We can’t just presume that people don’t want to participate: they are not being invited. Also, we have to recognize our role as researchers, clinicians, systems builders, and elected officials. Everybody has a role in what we have created here.

The other point I will make is the need for cultural humility. Again, we have people who are presenting with symptoms that might not be clear. The constellation might not be clear, but there is also a lack of humility when we are talking to people who might be presenting even with slightly different symptoms than those that we are already aware of for some of these rare diseases. So, the barrier is not necessarily the language of the individual patient or family, but it is our lack of ability to provide appropriate care services, interpreters, etcetera. I am very big on reframing this. It is not the mistrust or distrust of the population, it is the lack of trustworthiness of our systems of healthcare and research.

“We do not want to dismiss or forget that racism, discrimination, and bias built these systems that we are talking about. These are the same systems that historically excluded people from research, excluded people from high-quality healthcare, segregated care... All these things are built into the foundation of healthcare delivery and research.”

Nakela Cook:

I may just add one other point here, which relates to the specialty care that is unique and needed for patients with rare diseases. I think another compounding factor, when you start to think about populations that have been historically excluded, marginalized or minoritized, is that the access to those specialty care centers, specialists, etcetera, has already been shown not to be as robust and to be a challenge, especially for our chronic conditions that really require it. If you then compound what is needed for rare diseases, I think this becomes incredibly important, because referral to centers that have specialized care is essential in the care of rare

diseases. Being a cardiologist and thinking about specialty care, I just wanted to underscore this other additional important factor about our healthcare system, as it relates to people of color, people that traditionally don’t have access to these types of services on a routine basis. Having this sort of need, really makes it a much more complicated scenario for them.

Sean Sanders:

Nakela, could you please talk about some of the challenges of doing research in rare diseases and including people of color and people from these under-represented communities?

Nakela Cook:

Sure, I think it is an important question for us to talk about in terms of research with rare diseases, because many have focused on the fact that there aren’t treatments available for 95% of the conditions that we now think about in terms of rare diseases. At PCORI, we have focused on a research portfolio in the space of comparative clinical effectiveness research. I will give you a couple of points about why it is even harder in that scenario. We have a portfolio related to about 40 different comparative effectiveness research studies and methods studies – methods, because it is important to understand how you reach patients and individuals with rare diseases that may not necessarily be concentrated in one specific area, etcetera. You must think about how you reach them across the nation. Our studies have predominantly focused on those that have been priority populations such as racial and ethnic minorities, women, older adults, people with disabilities, or even those that may be in these underserved areas of the country, or potentially even those in those marginalized communities where there may be a lower level of literacy or numeracy.

We learned a lot from this type of research. We traditionally have found that sample sizes are a real challenge for very robust studies where you need a certain number of individuals to give you the kind of definitive results that may help to inform a treatment change in the clinical guidelines or clinical care practice. When you start to think about comparative effectiveness research where we typically compare more than one known intervention that can be efficacious, we often find that for rare diseases, there aren’t such interventions and very few to compare. So, we have had to go back to ground zero and think about some of the ways to address sample size challenges as well as try to figure out the types of things that may be in use that we could understand more about. One of the resources that we have used is a research network that is called PCORnet, that PCORI funds, to try to overcome some of the sample size challenges. It has a reach to many patients, electronic health record data and other types of sources, for us to observationally review what is happening in the treatment of rare diseases.

We have focused on comparing treatment modalities, or treatments with cross-cutting symptoms or screening practices. We are looking at treatments for cross-cutting symptoms that may be common among groups of rare diseases, to try to overcome some of those hurdles. So, we know that things like sleep disturbances, or pruritus, or comorbid other conditions can be common across rare diseases, and we are hoping to find clues there that could stimulate the discovery pipeline. So, it is a challenge in

terms of thinking about research for individuals with rare diseases, and compounded on that are the challenges that we traditionally have in trying to engage populations that have a lot of competing priorities related to their health, healthcare, and daily survival. We recognize that and use some special strategies around engagement that I can talk about a little bit later as well.

Sean Sanders:

Nakela and Consuelo, thinking about communities with food insecurity, high rates of poverty, or countries that are struggling simply to feed a large percentage of their population or are fighting communicable diseases, what are the reasonable expectations for funding and support of rare disease treatments?

Consuelo Wilkins:

When we are talking about people who are experiencing food insecurity, lack of economic opportunities, or other issues linked to social needs, there are many, many challenges. One of the challenges is that for many of them, it is hard to imagine what is the most important issue for them. They may delay to even present with their symptoms. People have, for many, many years, symptoms that might not necessarily be mild. They might be disrupting their lives, but their lives are so complex because of the structural and social barriers that they have to overcome. If you don't have food to eat, then you are not necessarily thinking about some symptoms that might be classic, such as mildly short of breath. If you think about Maslow's hierarchy of needs: what do I need at this very minute? Those are often quite challenging, but then they also co-exist with underinsurance, uninsurance, or other issues around access to care.

I would also like to re-emphasize Nakela's point about access to specialty care being so critical and important, not just for people who don't have insurance or are underinsured: having access to an insurance card is not equivalent to access to care. For example, the insurance card doesn't overcome the issues around access, such as if specialty care is in a part of town that is difficult for you to reach because you don't have transportation, or if you cannot take time off work without losing money, or if it is at an academic medical center where all of the historical abuse related to research and clinical care occurred... I think that is one of the biggest hurdles we have. Often, when we are applying for research funding, we are putting in costs for providing meals for people, even just for the day of a research study, but we are often heavily scrutinized and asked to take that out. We are overlooking the fact that participating in research costs an individual. So now, we are asking them to pay with their time or resources, but we don't provide anything for them! We have been able to do things like provide transportation to and from those appointments around research, but again, that is just a small piece of what people need to be able to survive. It would be great for us to be able to think more broadly about what people need to be able to participate in research. And of course, more broadly, what does health look like? And it is not just about a prescription or what happens in the clinical setting.

Nakela Cook:

One of the things I think is an opportunity to overcome some of these big hurdles is to really look to those who have lived experience with these challenges, to inform us on the best path forward. This is really where the work that I described as engagement comes into play. One of the things we hear at PCORI, where we really focus on engagement and patient-centered research, is that engagement of the patients, caregivers, and these communities that we are talking about, are really important in terms of understanding those affected and understanding what is really desired in order for them to be able to participate in clinical research or clinical care. The different settings where this may occur may need targeted strategies that are specific to certain people, certain populations, and a real understanding of those competing priorities that they are facing in their everyday life.

Many of the awards that PCORI has made that focus on rare diseases come from our engagement award portfolio, because we found there that individuals and communities, who often are thinking about these types of challenges, are looking for opportunities to bring people together in special convenings to talk about the treatments for diseases that may not be available to them immediately, but how they may access them, to think about patients and caregivers that are interested in developing communities of support and for advocacy purposes, and to help identify the research priorities that then we can pursue. Doing that through an engagement venue, I think, is a phenomenal approach.

One example is a sickle cell disease network project that we funded in Tennessee, which was an engagement project. The goal was to try to build capacity for individuals that were living with sickle cell disease throughout Tennessee to engage in research and patient-centered research as well as to try to build a sustainable sickle cell disease network in Tennessee that could serve as a conduit for driving patient-centered research and a healthcare service agenda. The outputs were the creation of a rural-urban sickle cell disease community-based network and a facilitation of different educational training sessions on research for non-research stakeholders (those that wanted to be engaged in research but weren't researchers, so to speak). Another output was a patient-centered conference on advocacy and implementation of outreach methods that were created by the community network. This is where, again, hearing a lived experience allows those that we are trying to understand that experience for to benefit from the research and other activities that we are supporting. The value is determined by them, and the engagement and activities allowed us to understand the research agenda that we could then pursue moving forward. I would be happy to talk about some of those other lessons learned from this type of engagement as we go through the conversation.

“One of the things I think is an opportunity to overcome some of these big hurdles is to really look to those who have lived experience with these challenges, to inform us on the best path forward.”

Linda Goler Blount:

If I could just amplify what Nakela and Consuelo were saying... We happen to be a grant recipient of PCORI for a program we created called TEACH, Trained Empowered Community Health Advocates. The purpose is to understand the lived experiences of Black and Brown women to help them better negotiate and understand what the clinical trials process is about: how to participate in a way that is respectful, where you feel valued, because we were hearing that those who happened to participate felt like they were being tolerated in many cases. So, understanding the lived experiences and building that into a training program has been really helpful. The RDDC is very much focused on understanding what that experience is like. The informed consent process, for example, is probably burdensome for most participants, especially for low-income participants and participants of color. It is designed to protect the institution. Maybe there is an opportunity to rethink how to make it less burdensome for clinical trial participants. Of course, we must look at the pipeline: the percentage of Black and Brown researchers and those who have received R01 funding from NIH hasn't changed in 40 years. The FDA has some diversity guidelines around clinical trials and research, but they are not enforced. We therefore have some opportunities to make some changes to help broaden the tent, and to make people feel more included and valued. If they do, I think the outcomes will be better.

Jamie Sullivan:

I will add that our policies in the US aren't set up to facilitate easy participation in research. We don't have great paid leave, we don't pay caregivers for the work that they are doing, we don't have great home care coverage or even childcare. We hear from patients who simply can't take another day off work, or their caregiver can't take another day off work. We hear from patients who have two children, one of whom has a rare disease, but they can't go participate in a day of research at the clinic without a place to bring their second child. Our system and our federal policies or state policies aren't set up to even help, once we can overcome the barriers that you have heard about from Nakela, Consuelo and Linda.

Sean Sanders:

We have spent quite a bit of time talking about these barriers and these challenges. I would like to turn to what is working. Linda, what are some good models and good examples of what is working? Where can we look to find those models that we can apply elsewhere? Are those models portable?

Linda Goler Blount:

I wish I could say there were dozens. I probably can't do that, but there is some hope. I mentioned the TEACH program, but there are also examples of academic community partnerships. We worked with a group out of San Jose, California, on something we call "Tech to Equity", where we wanted to bring research to address the needs that the community had defined rather than the needs that researchers had defined. So, the community group in San Jose conducted its own health needs assessment, and they went to the research community in California and Santa Clara

University and a couple of other universities to say: "Here are the issues that are important to us, here is what we think needs to be done to help improve outcomes and the overall health status in these communities". This isn't rare disease-specific, but it certainly could be applied in the rare disease space, as advocacy groups come together to help identify the issues and talk about their own experiences. It would take researchers and academic institutions to be willing to listen to them, to value their opinion, to take their own sort of fundamental research seriously and then act on it. So, it is possible, but we would have to see a change in the standard approach to academic research so that the community is included, valued and seen as a part of coming up with solutions to their own concerns.

People have heard me say advocacy is a luxury. You must have time and money to be able to be an advocate. Oftentimes, Black and Brown people and low-income people end up being marginalized by researchers and by clinicians because they are not out there advocating. As we have heard, they have got to work, they have got childcare responsibilities, they may have other responsibilities. They simply don't have the time or the resources, which doesn't mean they don't care deeply, but they don't have the luxury of the time and the money it takes to be an advocate.

"Advocacy is a luxury. You must have time and money to be able to be an advocate."

Jamie Sullivan:

I will talk a little bit about one program that I think everyone points to, which is probably the most equitable public health program, although it has a lot of room for improvement: that is newborn screening. You could say similarly about some of the new initiatives that have started to pilot, universal whole genome sequencing for certain populations such as NICUs that have unexplained symptoms. But newborn screening is often held up as one of the most successful public health programs because it is supposed to be universally accessible to every baby born in the US. Truly it is a great success. However, there are certain areas where we know we can still do more and do better.

One thing that Linda just said stood out to me in that you need resources and money to be an advocate. Well, one of the ways the newborn screening system is set up is that the Federal panel makes recommendations on what conditions to include. That nomination process takes over a decade, it often must be led by patient advocacy organizations who then need resources and champions on their side to help get them through that process. Once the federal panel finally says, "Yes, we think this condition should be added", it requires advocates to go state by state and advocate for their condition to be added to the panel. Just the process to get this condition added to the panel can have some inherent inequities in it.

Also, while every baby should be screened, that doesn't mean that every baby has the same chance at benefiting from the care and the therapies that are available following the screen. So, we have a lot of room to improve in the follow-up services in how families are connected to care, and what is available in terms of culturally competent care. Genetic counseling is a great example:

genetic counselors, who listen to rare disease patients, are so critical to help them understand and start their journey, and try to find treatment and understand what it means for their family. And yet, only a very tiny fraction of genetic counselors is coming from the non-White population. There is a ton of room to do better, but I do want to say that newborn screening is certainly a good model, a beneficial model, but I hope that we can all work together to make it as beneficial as it possibly can be.

Consuelo Wilkins:

I would say advocacy is often a luxury and for the privileged. I have worked with a number of really amazing advocates, especially parents. Particularly, often, they are mothers of children with rare conditions; this is their entire life. They spend almost all their time doing it, and not everyone can afford to do that. It is very challenging for those who are doing it, but to do the work, you must have at least the chance of being supported in some other way. They are often people who have a higher level of educational attainment, they have been able to negotiate access to different circles. They can get their talking points together; they go sit in front of their elective officials...

There are so many things that have been set up there, but I will credit PCORI for really helping to shift this in many ways, because bringing the spotlight to the attention that these roles need to be paid, especially when we are partnering, and that people need to be compensated, is something that many advocacy organizations have just not done or even embraced. It is like, “no, no, all of the dollars we raised need to go to the research”, and we are not always thinking about who is being left out.

Also, to emphasize Jamie’s point: we can advocate for these resources and screenings, but not everyone can benefit the same way. It is not just about access to care and services. If we start doing broad whole genome sequencing on newborns or whom-ever is presenting, we must be able to tell people that if you are from a population who is not of recent European ancestry, then the likelihood that you are going to have variance of unknown or undetermined significance is going to be much higher. Our history with not having equitable and inclusive research is making it even more challenging for these populations as we move forward. What does that mean for how we do this research? Are we going to build in strategies and plans for when we do have more evidence and understand what these variants mean or might mean? Are we re-contacting families? How often are we going back into the databases to see what else we can glean and learn? Who is communicating that information to these populations? How can they have access to it? There are lots of other things that we need to build into the structure to try to repair the damage, the historical and ongoing exclusion of these populations. We must work on that.

Sean Sanders:

Great, thank you so much. Nakela I would like to give you an opportunity to speak as well. I know it is in your wheelhouse.

Nakela Cook:

Certainly. Firstly, I would like to add something related to one of the points I mentioned before in terms of some of the lessons that we have learned that have worked when we talk about engaging these populations in research that have a lived experience that we can learn from. One of the things that we talk about with engagement as a model is that it is inclusive in identifying the research priorities that are important to a specific population, as well as involving them in the conduct of the research and in the dissemination and implementation of the research findings. Over the last 12 years or so, we have learned that engagement gives the opportunity to make the clinical research reflect the needs and the values of the patients, the caregivers, the clinicians, and other stakeholders. We have learned the importance of compensating people for this type of engagement to allow their voices to be heard and to see them as equal partners in the research enterprise. I think that is incredibly important for making sure that this is considered to be a valuable opportunity for those that were trying to benefit with the work that we are supporting.

“Over the last 12 years or so, we have learned that engagement gives the opportunity to make the clinical research reflect the needs and the values of the patients, the caregivers, the clinicians, and other stakeholders. We have learned the importance of compensating people for this type of engagement to allow their voices to be heard and to see them as equal partners in the research enterprise.”

We have also learned that engagement and research helps to improve the feasibility of doing this type of research in real world settings. As it relates to rare diseases, one of the things we talked about were some of the challenges of sample size for research. Moving into real world settings or trying to figure out how to do that when you are dealing with the issues of transportation, child-care, the competing issues of costs. We know that individuals with rare diseases have much higher medical and out-of-pocket costs and economic burdens and others. So you must understand that through engagement in order to make the research feasible.

“We know that individuals with rare diseases have much higher medical and out-of-pocket costs and economic burdens and others. So you must understand that through engagement in order to make the research feasible.”

Thirdly, we want to make sure that the research that we do is relevant to the population that we are interested in benefiting as well as encourage the uptake and use of the findings. As we have heard, engagement makes the research worthwhile in those aspects. I think that it is truly important, when we are talking about

patients who may have a lived experience that is considered rare, that we must truly engage to understand several of these aspects. I think some of the benefits of this type of model for thinking about research in the setting, are that we actually have an increased knowledge about what we can do that is more effective, but also, patients, their caregivers, and others, feel like they have an increased knowledge, as well as more enthusiasm for the research, even when they may be dealing with these large competing priorities that we have talked about. To build on a point that was mentioned earlier, it will also help improve the trustworthiness of the researchers in the clinical enterprise, which I think is important, when we start to talk about communities that have been historically excluded or marginalized. I think we couldn't have a better understanding of real-world experiences except through the lens of those that have been affected.

Sean Sanders:

Thank you all very much for those comments. I just wanted to touch on the use of technology and how it can help. For instance, we have talked about the challenges with patients getting to a clinic to participate in a trial. Telemedicine, that has seen a rise during COVID, seems to be much more accepted now as a way to talk to physicians and clinicians. Any thoughts from the panel on how technologies such as telemedicine and AI might impact how we are thinking about this?

Linda Goler Blount:

I think technology - data science, AI - has great potential. However, we must be careful and cautious. During the height of the COVID epidemic, two years ago, we saw that pulse oximeters didn't work as well on people with dark skin, we saw that Dexamethasone wasn't as effective in African Americans. That wasn't a surprise as when did the research, there were no Black people involved in the trials of that device or that medication. So, I think we must be careful when we think about the role of technology. I happened to co-author a paper a couple of years ago, in which we looked at bias in the machine learning algorithms of the EHR scheduling systems. It turns out that the AI in the scheduling systems was double and triple booking Black patients. There were probably no Black people involved in the development of the machine language or the code, and one wonders who was involved in the testing. So, while this technology was considered an efficiency-producing technology for the optimal operations of a practice, people didn't see that Black patients were being double and triple booked. This means they probably weren't coming back, which has implications for their outcomes: if they are not coming back, if they don't have the time, as it has been said, because they can't take time off work, because of child care issues, transportation, or whatever, if they can't come back and wait for hours, then they may never be seen, which means their conditions may never be addressed.

Therefore, I think we need to be careful about putting too much credence into technology. But there is an opportunity to look at what has gone into the technology, what has gone into the machine learning, what has gone into the algorithms and create opportunities to be more inclusive. One of the things we have been

talking about are strategic research committees that work with technology producers as well as obviously hopefully improving the pipeline, so that when the testing occurs, it is inclusive, and we can talk about it being effective for everyone and not just a certain segment of the population.

“But there is an opportunity to look at what has gone into the technology, what has gone into the machine learning, what has gone into the algorithms and create opportunities to be more inclusive.”

Consuelo Wilkins:

I would like to add to Linda's outstanding points. The data that we are using to create algorithms is biased. It is based on these systems of exclusion and exclusionary care practices. We must have people who are doing the research understand what those biases are and think about how to mitigate them. We have still dozens of algorithms that have faulty race corrections and modifiers that, again, are built on racism. We also don't really know what race or ethnicity might be a proxy for. If we accept that these are social constructs, then what are the social and structural factors that we haven't quite captured that those are actually serving as proxies for in these algorithms? Balancing that, do we remove them? But then, we are missing those still key aspects.

“The data that we are using to create algorithms is biased. It is based on these systems of exclusion and exclusionary care practices. We must have people who are doing the research understand what those biases are and think about how to mitigate them.”

Also, just a word about telehealth and telehealth equity during the pandemic, and trying to think about how we would serve these populations that have been marginalized and minoritized. Telehealth provided some opportunities, but we were also still trying to force people to use telehealth the way that privileged and resourced people use it. We must learn to be a little more flexible and look at what that looks like, what kinds of apps are required, how much paperwork people have to do before on their tiny device as opposed to people who are having their visits via a computer, which is very different. If you have to go outside to take your visit because you are working in a job where you don't have a desk and a closed door, what does that look like? How is that different? We also all often talk about this digital divide, but many of the populations that we are talking about are very tech savvy. They use their devices for many things in many ways. They just don't use it the way that we think they should or have planned for them to use it around healthcare and research. So, if we would just open our minds to allow them to partner with us so that they can actually design those approaches and strategies, we would probably be a lot more successful.

Jamie Sullivan:

I think we saw some great benefits during the initial period of flexibilities and increased use in telehealth in rare diseases. We also probably missed an opportunity to gather more robust data on how it was being used and how it may or may not have been improving some of the challenges experienced by rare disease patients. But what is the promise of telehealth in rare disease? When we asked patients what some of the most important benefits are, the response was: being able to connect with a specialist out of the state that they live in, especially for those with rural locations or those who have a disease where there is one specialist in one city in the US. Prior to the pandemic, they couldn't connect with that specialist: they have mobility challenges, they are unable to travel or to afford to take three days off work, but maybe they could have taken half of a day off work, or a couple of hours to be in an appointment. Traveling to these centers is just not feasible. Those patients, for the first time, were able to connect with those specialists via telehealth. The policies that were waiving the requirement that an individual must be an established patient of the provider to receive telehealth services and be in the state where that provider is licensed.

Unfortunately, as we have carried on throughout the pandemic, some of those policies have been rolled back. The most potentially beneficial policy to a rare disease patient, that they could see physicians out of state, by and large, has gone away. That flexibility has gone away, and we have reverted to a system of state licensure being required. It is simply not feasible for so many medical providers to go state by state by state and try to get licensed. That is if the state has allowed their patients to receive care out-of-state regardless of whether they are licensed or not. These policies are impacting everyone, but certainly, for those who are receiving health care benefits through Medicaid, it has even more of an impact. So, we risk losing some of the potential benefit that we have gained over the last couple of years if we don't get our telehealth policies right.

Nakela Cook:

I think some of the comments about the promise of telehealth being very real are informative, but some of the perils that have been emerging, that we are recognizing, really invite us to think about how we understand telehealth more effectively, how we design it, etcetera. I think there is an important research agenda here as well. We have seen in some of the studies that have come out during the pandemic, such as the one by RAND, that actually saw that the increases in the use of telehealth during the pandemic were mostly amongst individuals who are insured, more affluent, and more in metropolitan areas as compared to rural areas. When looking at low-income individuals, in this scenario in California, they found that the telehealth visits were audio only for the majority as opposed to including video. We must understand what those implications are in terms of how different types of telehealth visits affect care outcomes.

I think there is an important research agenda, and some of the data that was coming out from surveying physicians actually highlighted that there were real challenges in implementing this in terms of reimbursement, technology challenges for patients as well as the integration into the electronic health records, especially for individuals that need coordinated care. That is an important component of delivery of this type of service. We need to overcome these types of challenges to see the benefits and for the potential promise of telehealth to come to fruition.

Sean Sanders:

Thank you to a fantastic panel, I have learned so much from you and I hope that our audience has as well. Goodbye everyone.

The urgent need to internationalize databases for rare disease patients

There are multiple barriers to rare disease diagnosis, including access to testing technologies, availability of knowledgeable health care providers, and lack of uniformity of the phenotype for a given genotype or disease-causing agent. These barriers significantly lengthen the time between detection of a rare disease and its diagnosis, aptly called the diagnostic odyssey.

The collection and sharing of accurate, standardized data are key priorities in shortening the diagnostic odyssey. Social media platforms, with the correct protections, could also help in this regard. Instead of individual health care professionals learning case-by-case and in isolation, they would have access to a comprehensive database that could be a vital and life-saving tool. Imagine how a rare genetic defect with a specific phenotype found in a patient in Uganda could quickly be linked to the same mutation identified in Sweden, China, or Afghanistan. Instead of being treated in isolation, the shared knowledge on standards of care could be transmitted instantaneously, benefiting the physician, patient, and family. Consider also the potential if a biopharma company with a promising therapy could commit to developing it because of an international database that shared relevant information and patient numbers.

At present there is no international database on rare disease genotypes, no standardized nomenclature for phenotypes, and not even an agreed-upon consent process to acquire, store, and maintain such data. This deficit disadvantages patients and thwarts the development of new therapies. A universal approach is needed to gather, store, and share phenotypic and genotypic data for rare diseases. We require an accepted, trustworthy system that protects patient identities while sharing critical data needed to advance diagnosis and treatment. This webinar will interrogate global experts on how to drive this unmet and urgent need forward.

Panelists



Lucia Monaco, Ph.D.
Rare Diseases International,
Milan, Italy



Peter Robinson, M.D., M.Sc.
The Jackson Laboratory,
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Eric Sid, M.D., M.H.A.
National Institutes of Health,
Bethesda, MD



Domenica Taruscio, M.D.
National Centre for Rare Diseases,
Rome, Italy



Sean Sanders, Ph.D.
Science/AAAS, Washington, DC
Moderator

The Conversation

Sean Sanders:

Hello, and thank you for joining us for this fifth webinar in our 2022 Science and Life series on rare diseases, entitled Knowledge Is Power: The Urgent Need To Internationalize Databases For Rare Disease Patients.

Domenica Taruscio:

My name is Domenica Taruscio. I work at the National Health Institute, the Istituto Superiore di Sanità, in particular at the National Center for Rare Diseases. I am a medical doctor, histopathology by profession. I performed my postdoc at the Yale University in human genetics.

Lucia Monaco:

I currently am a volunteer policy advisor for Rare Diseases International. Previously, I have chaired the International Rare Diseases Research Consortium for the past three years, which I joined since its inception back in 2011 in representation of my organization Fondazione Telethon, an Italian charity that is funding, supporting, and developing research for rare genetic diseases, after more than 20 years as a researcher in the field of rare diseases.

Eric Sid:

My name is Eric Sid. I am a Program Officer within the National Center for Advancing Translational Sciences at the National Institutes of Health in the US, NIH. I work primarily with our public health programs that are focused on rare diseases within our division of rare diseases research innovation. I am glad to be here as part of this panel today.

Peter Robinson:

I have degrees in computer science and medicine and practiced as a pediatrician and medical geneticist at the Charité Hospital in Berlin, Germany. Since 2016, I have had a genomics bioinformatics position at the Jackson Laboratory for Genomic Medicine in Farmington, Connecticut.

Sean Sanders:

We have a wonderful breadth of experience here today. Domenica, could you please tell us what is a patient registry or database? What does it do? How is it used in research and by clinicians?

Domenica Taruscio:

A registry is a well-organized system to collect standardized information on a group of patients who have a specific disease or condition. They were traditionally established by a research

institution or academics, but since several years, they are also established by patients. They collect several information, which should be standardized, but we will develop this issue later. Patient registries collect clinical data, genetic data, biological data, and are sometimes linked to biobanks. The objectives of the registries are wide. They may collect information, for example, to study the natural history of a disease. They develop research questions in order to push research. They may monitor the safety of a drug, or they may, for example, develop standards of care and monitor and improve the quality of life of patients.

“A registry is a well-organized system to collect standardized information on a group of patients who have a specific disease or condition. [...] Patient registries collect clinical data, genetic data, biological data, and are sometimes linked to biobanks.”

It is very important to correctly set up a registry. A registry is not really a database, it is quite different. Registries should rigorously follow quality of data and quality of registry. Quality of data is a part of the quality of the registry. Nevertheless, the team should be trained to have a correct case definition of the disease or the condition that we want to focus on. We should define the target population; we should also correctly identify the data source and then control the duplicate of cases. Most importantly, we should use international standards for coding, for nomenclature, data entry and so on. Finally, this instrument should give accurate data and information to foster research, for the benefit of the research but also essentially for patients.

Registries are tools which should be complete, otherwise, they are not very useful. The international community is now pushing for data to follow the FAIR principles, standing for Findable, Accessible, Interoperable, and Reusable. To avoid the creation of silos among the different instruments, we should, depending upon the condition, give the possibility to share data and make data interoperable.

“The international community is now pushing for data to follow the FAIR principles, standing for Findable, Accessible, Interoperable, and Reusable.”

Sean Sanders:

Thank you, Domenica, you have touched on a lot of points that we will be covering through the rest of the webinar. The usefulness of the registry will very much depend much on the quality of the data that comes in. Lucia, I know you deal with biobanks: what is the role of biobanks in these types of registries? How is that data moved from the biobanks into a patient registry?

Lucia Monaco:

Yes, biobanks are a very important aspect of collecting information, but not only information from patients. Biobanks collect biological material from patients that live with a rare disease. This biological material needs to be associated to data that is accurate, complete, and standardized, as Domenica mentioned for registries. Biobanks are a fundamental resource for research on rare diseases because due to the rarity of patients, being able to conduct research on the actual biological material is really challenging, especially for some ultra-rare disease. The underlying principle that the international community is trying to adopt is to make biobanks internationally accessible and make the biological samples visible, accessible, and distributed across different countries. To do so, several international programs have been launched and set up. I will speak about European programs since we are based in Europe.

The initial seed for a network of biobanks is Euro Biobank Network, that became the network of a bigger European program called RD-Connect, whose main goal is to link the data and information coming from registries, from biobanks, and very importantly, from the omics area, so that the patient is at the center and as the main source of the information of the biological material and all the data that can be connected all together. The program RD-Connect, has now been taken up by the European Joint Program on Rare Diseases and the virtual platform for resources that is being developed there.

Sean Sanders:

Peter, could you please talk about some of these genomic databases? How are they working? What successes have been achieved? Could you also talk a little bit about where the gaps are, or what is missing?

Peter Robinson:

In the context of standards and fairness, as explained to us by Domenica, it might be good to start with a simple example. 20 years ago, databases were not FAIR in the field of human genetics. For instance, let's take amyotrophy. It is a medical word that means muscle wasting. There are a total of about 10 different synonyms for that word, such as skeletal muscle atrophy. If different databases are using different words to store the same concept, then computers cannot exchange information between those databases. Therefore, it is very important to get all the databases, all the registries, all the resources in the field to agree upon how to call things.

“It is very important to get all the databases, all the registries, all the resources in the field to agree upon how to call things.”

My group has been involved in the development of the Human Phenotype Ontology. It is a hierarchical structure of concepts with definitions and synonyms that not only provide a standardized way of naming things, but also allow you to use that as a computational tool. For instance, if you wanted to find all samples in a database or a biobank that have an abnormality of muscle,

there are hundreds of different abnormalities of muscle, and they all have different ontology terms. However, you can roll them up in a search using the hierarchy of the ontology to find all those samples at once. That is one important thing. Another important item is how to arrange this information because it is not always the case that you are just interested in one single concept such as skeletal muscle. You might be interested in finding all patients that have a mutation in a certain gene and have an abnormality of skeletal muscle. Therefore, you need a schema, a structure of how to arrange your information to send to the database to perform that query.

A project that we have been involved in with the Global Alliance for Genomics and Health is called the Phenopacket Schema (<https://phenopacket-schema>). It is essentially a schema that has slots for phenotypic features for numerical measurements, for treatments, for genomic findings. This is part of a much larger suite of standards that the Global Alliance, the GA4GH, is preparing for all aspects of genomics data. If one can imagine that databases across the world have adopted these standards and these ways of exchanging information between computers, so-called APIs, then with one query, you could basically ask biobanks all across the world for samples relevant for your experiment and find them in a much more efficient and fast fashion than if you had to formulate a different query for each of 10 biobanks that you wanted to learn from.

Sean Sanders:

The NIH is deeply involved in researching and treating rare diseases and is also very interested in this topic. Eric, what is the involvement of the NIH in this topic? What successes have you seen in setting up these registries?

Eric Sid:

I will piggyback on something that Lucia said earlier, which was that registries are about how you center patients in this discovery process of research. Often, when I am talking to patients about registries, I like to think about stories, and registries are tools to help convert stories into data. They provide the structure necessary for researchers to ask the questions the individual stories might be sharing, and to look at a population-wide question. I often use the following example for patients : all of us have meals that we have grown up eating, that we want to be able to pass on to our children or to others. We talk about those meals using recipes. We use standards, for example, for measuring: grams versus pounds, ounces, milliliters, and cups. These different tools and standards help us then to give the same exact instructions on what we are doing each time to make these meals. Oftentimes, many patients can easily express their stories either in person or via social media, but the real question is how to convert that into some type of data or structure, to allow us to bring all those individual patient stories together to find meaning.

“Registries are about how you center patients in this discovery process of research. [...] Registries are tools to help convert stories into data.”

The NIH finds that we must be able to help innovate and create meaning within rare diseases, starting at the beginning of creating the natural history and understanding of a disease. The starting point is understanding how a disease affects not just one patient, but many different patients that might have that disease and how that affects them over time. Again, the stories of each individual experiences for each patient and their family then allow the questions that we are asking to be asked for each other person involved in that registry. Compiling that all together allows us to then get a sense of how a disease progresses in its natural state for everyone that has it over time. Peter mentioned different ways that we can start to structure and standardize that. This adds together into our body of knowledge. Researchers can then start asking questions such as: are they eventually aiming towards a treatment? What is the difference that would happen with this treatment compared to what naturally normally occurs if you don't have a treatment for that disease?

Domenica Taruscio:

I would like to underline that developing a data registry is time and resources consuming. Therefore, I think it is crucial to establish a good team to develop a good registry. There are several rules to do so. Firstly, I encourage scientists or patients that are willing to start to maintain a registry to have quality assurance. This means that they should establish a governance. A governance system enables to clearly define the objectives of the registry (main and secondary objectives), to make it specific rather than generic.

“Developing a data registry is time and resources consuming.”

We should also identify the stakeholders, including patients that are active “actors”. We need to build a team that is dedicated to this tool. We then need to approach the ELSI problems, ethical, legal, and social issues, including privacy, which is very important. There are different rules related to these issues among countries, and if we want to share data at a global level, we must take these issues into account. Finally, sustainability is critical: sometimes we see a great registry, to which scientists are dedicated, but it is halted because it is not sustainable.

In this framework, it is also very important to continuously train the team, because the team should know what the case is, the correct case definition for a disease, which are the correct data sources, which is the correct geographic coverage, and so on. There are therefore several rules that we should follow to have high-quality data for high-quality studies, which can foster research and serve as a scientific tool for research.

Then, setting up IT infrastructure following the well-established FAIR principles is also key. Furthermore, data quality is crucial, and it is different from the quality of the registries: it is inside the quality of the registry. We should then disseminate this information, because patients collaborate, and contribute, but they also want to know how their data is being used. Information should be published through a peer review publication or any other document. Finally, I also recommend to perform external audits to ensure good quality data.

Lucia Monaco:

Going back to biobanks, everything that Domenica said applies to biobanks, every single point is important. In addition, we need to consider that biobanks have the additional “physical” nature of biological samples. The way in which these samples are collected, stored, and the processes are very important, and standardization is fundamental to ensure reproducibility of experiments.

Think of experiments being set up with samples coming from a very different biobanks because patients are so scarce and are scattered in different labs in different countries, sometimes in different continents! Therefore, having robust standard operating procedures that are shared among biobanks is very important. There is a set of these SOPs that are, for instance, published on the website of the Euro biobank that I mentioned before, but there are also other places where you can find these standard operating procedures. It is fundamental that the investigators who will receive the samples know exactly how the samples have been prepared and treated so that they can rely on the results of their research.

Finally, the sustainability is doubly important because biobanks do not only deal with data, but also with a structure that will collect, preserve and work out the samples work before distributions. Very often when thinking about funding for rare diseases research, these kinds of infrastructures are disregarded or neglected despite being so important.

Sean Sanders:

So, this all feels a little bit overwhelming as somebody who is outside of this. It seems like there is so much that is needed to set up one of these registries. Eric, if somebody or a patient group wants to set up a registry, where do they go to find the information to get these best practices?

Eric Sid:

Yes, it is a great question. I would encourage patient advocacy groups and patient leaders that are starting to get organized to consult some resources that both NCATS and other agencies have made available. One of them is called the Rare Disease Registry or RaDaR Program. You can find that at <https://registries.ncats.nih.gov/>. It just provides some general language on understanding the background behind registries and how to get started in the process of organizing your community to start developing a registry (at the very least, a contact registry).

Registries may seem overwhelming. Domenica provided a great overview, but there is so much to un-package there, that I find myself thinking of the fact that there are so many steps involved in that process very much like you, Sean. The RaDaR tool that I was mentioning earlier provides a stepwise process to get involved as a patient organization on moving forward with the development of a contact registry. But the important thing is to understand: what is the research question that underlies this registry that you are starting to build?

For example, one of the things that I oftentimes find limited amongst many of the rare disease registries that I have looked at is that not all of them will ask questions about demographics, such as, race, ethnicity, or the background of the individual participants

in that registry. As someone who is looking into understanding equity issues and disparities amongst different rare diseases, it is an incredibly important data point for me to see how diverse the population may be in that registry. From a patient's perspective, that information is incredibly useful because that might help your community say, “Well, maybe we are collecting information from one group, but not from another. Are we asking everybody what language they speak at home? Do we have our registries forms available in those languages?” Those are easy ways to start to see that there may be gaps in the research questions that we are asking. You need to try to understand what you would want this registry to investigate upfront. Therefore, starting with a good framework, having a good understanding – and just understanding is a marathon, not a sprint – and starting to build some of that data collection at the beginning point with some good standards and understandings is important to start this process. Again, I would encourage some of you to look at those resources if you have any questions about how to get started.

Peter Robinson:

One thing that I think is important to understand about registries and their use to understanding rare disease treatments is the fact that if you are doing this study on a common disease, you can easily find a 100 or a 1000 or many thousands of patients to test a new medication. This means that the statistics, the mathematics that you use to determine whether a treatment is better than another, or than placebo, work better. In general, it is a rule that the more data you have, the more power the statistics have. However, rare diseases, by their nature, are rare, and so typically, you have many smaller studies with 20 patients, 50 patients, or less that are barely enough to get statistical power.

Therefore, I think one of the goals moving forward is to combine the results of individual studies. This has been very difficult for several reasons. One of them is that typically, clinical studies on rare disease do not make the primary data available. These studies are often paid for by the pharmaceutical industry. If successful, they are typically published as a paper but not in computational form that would allow you to easily search over that or do a secondary analysis, and many studies never get published at all.

Another issue is that to combine results from different studies, you must use comparable outcome measures. Just as an example, when you give a patient, let's say, a muscular dystrophy treatment, you are not measuring, if they get better or not: you can't really measure that. You must measure something specific. For instance, you could measure how many meters a patient can walk in six minutes, or you could measure how long it takes for a patient to walk 100 meters. They sound like they are the same thing, but it is statistically not possible to just combine data that are using different measures. Therefore, the community has not really agreed on what the recommended measures are for treatments. There are some attempts, some common data elements, but in general, there is still a lot of heterogeneity that is preventing us from combining effort. So, I think we really need standards. We need some way of sharing the data from a comprehensive collection of studies, performed in rare disease patients. And we need some agreement as to what we are measuring.

“I think we really need standards. We need some way of sharing the data from a comprehensive collection of studies, performed in rare disease patients. And we need some agreement as to what we are measuring.”

Sean Sanders:

Some of the challenges that Eric was talking about, such as language barriers and cultural barriers, must be compounded when we are internationalizing these registries. Lucia, what are some of these additional challenges that are specific to internationalization? Also, Peter covered the fact that there are very few patients, but are there any other specific challenges for the rare disease community?

Lucia Monaco:

Well, let me start with a very basic problem: even the recognition and official identification of a disease as “rare” at country level is uneven across the world. This makes it quite difficult, firstly for patients to be recognized as rare disease patients, but also everything that is associated with their status, and so, their inclusion in registries at the national and international level. For this reason, Rare Diseases International has started a working group and has worked at proposing a definition of rare disease, to provide a set of guiding principles that could be taken up by countries that still do not have official definitions of rare diseases. I think that is very relevant. Living in the Western part of the world, that may not seem like an important problem, but it is in a larger portion of the globe.

Having said that, the issue of language is also very important. We are all familiar with and automatically think of English as the language that is used for exchanges, however, there are efforts to produce resources in different languages to allow different populations to have access and to benefit from the whole pipeline of knowledge, data collection, research development, and so on. This is something that has been taken up by IRDRC, the International Rare Diseases Research Consortium, where a dedicated task force has specifically addressed the difficulty of indigenous populations to have access to diagnosis of a rare disease due to the important language gap, despite the fact that part of the country’s population is indigenous, making indigenous populations invisible and untreatable. So internationally, there are many efforts to address these issues. Of course, it is a huge problem, but any small step forward is important because it can serve as an example and serve as a seed for further development.

Eric Sid:

Domenica mentioned several great points earlier, and I just wanted to call attention back to the concepts of sustainability and governance. I think those are incredibly important issues. When you are talking about a rare disease, and thinking about the registry that underlies some of the research that is occurring in that rare disease, researchers may come and go. Their projects may extend for very particular points of very niche questions within a

disease. They may then come to the next project, and then move on to another disease. It is important to encourage a close collaboration between researchers and patient advocacy organizations to provide a whole framing governance model which allows to look at all the different types of research that are needed within this disease. Going back Peter’s point, it is important to think about the standards required for different researchers but also for the disease community to be able to progress with the research in that field.

Thinking about this in the long term, you don’t want to make a registry dependent on a single researcher or maybe even a single organization. You should have several partners involved thinking about how it should be managed in terms of the research direction for the disease.

“You don’t want to make a registry dependent on a single researcher or maybe even a single organization.”

Domenica Taruscio:

“Registry” is just one word, however, it is a complex concept. For this reason, at our institute, Istituto Superiore di Sanità, which is based in Rome in Italy, we started in 2014 an international summer school on rare disease registries and verification of data. In few days, we will start the new 2022 edition. It is very important to train not only professionals, not only medical doctors, or curators of registries, but also patients. The summer school is open and free of charge for all interested persons, stakeholders, and teams that are willing to start or maintain a registry. The teaching language is English. I understand the fact that, as Lucia said, there are several language barriers, nevertheless, we must use at least one common language, which is English.

It is important to learn theory. Therefore, the first three days of the course are dedicated to governance, sustainability, ELSI and so on. The last two days are practical activities. We call it “bring your own data” and you verify your data. I believe that we need these kinds of examples all over the world if we want to create an international community which is working together. Please join the efforts and let’s continue together. Thank you.

Sean Sanders:

Could we talk a little bit about the critical factors for data collection? Peter, how is balance achieved between collecting sufficient data but not over collecting data? What factors should be considered when we are collecting data? I am thinking about ease of collection, burden to the patient or the clinician, but also variations in terminology and practice...

Peter Robinson:

Well, that is an enormous question, and it really does depend on the context of each individual project. Experience has shown that collecting clinical data is the most expensive and most difficult part of any clinical research project. This is because the electronic health record systems that are in use are simply and obviously

not designed for research, and in many cases, they are better adapted at billing than at supporting patient care. For this reason, there are basically two strategies. One is to ask clinicians or other curators to enter data outside of the actual clinical records. In medical genetics, in human genetics, there are tons of programs that allow you to enter human phenotype ontology terms and many other kinds of data.

“Experience has shown that collecting clinical data is the most expensive and most difficult part of any clinical research project.”

The other approach is to try to extract data from electronic health record systems basically doing the best that you can, and there are tons of approaches that do this. Typically, though, it is difficult for rare disease because the features that we are interested in rare disease are often so rare that they do not have codes in the electronic health record such that they are written in free text in a clinical note. This means that you are required to use text mining. Text mining can be up to 90% accurate on published medical texts, but if you go into clinical texts from a hospital, there are so many other things going on that the accuracy drops to 60% or so. Just as an example, we are doing text mining of clinical records, and in a new project, we initially found that many people were found to have myocardial infarction heart attack, which is strange. When we looked at the data, we saw that many of the records had a warning: “if you have a myocardial infarction, call the emergency number”, which in the US is 911. But that wasn't a finding about the patient! So there are many things like that that make it currently very difficult to extract the information you need for rare disease research from electronic healthcare systems.

Domenica Taruscio:

I suggest establishing a general registry (for example, population based), with a common data set. The set of data would be transversal, in common with many rare diseases. Starting from there, you can develop tested registries, which means disease-specific registries. So, you would have a general registry: for example, in Italy, we have a national registry for rare diseases which covers more than 500 rare diseases. Of course, we collect less data. But from there, we can generate specific registries, in which you can collect specific variables for a specific disease and you can go deeper. I believe this would be a useful strategy.

“I suggest establishing a general registry (for example, population based), with a common data set. The set of data would be transversal [...]. Starting from there, you can develop tested registries, which means disease-specific registries.”

Eric Sid:

I agree with Domenica. I like to think of it almost like a three-course meal. What you are thinking about is that everyone may

have the same main entry, but you might want to adapt different types of modules or different types of appetizers, desserts as needed. You may have some general questions you are asking in common, and then, as new research opens new opportunities, new questions, you add to that.

Domenica Taruscio:

This is a great and powerful tool as it allows to have several specific disease registries for specific research questions. But then, again, you need human resources, economic resources, and sustainability.

Sean Sanders:

Eric, when someone is querying the database, what are the challenges there with finding the right information? Is there a way that databases or registries can be set up so that the queries are more easily done or that the data that comes out is more valuable?

Eric Sid:

I will turn back to first thinking about governance, because part of the question you may want to also be asking is: who has access to the data? Therefore, it is important to make sure it is not just starting from researchers, but registries are really including researchers, patients and patient advocacy groups. The reason I mentioned that is that first and foremost question you need to be able to ask is: how is the framework that you are setting this up? You might be asking if some of the data that might be gathered is proprietary, if it is accessible to everybody, or if it is only accessible to those that maybe belong to a certain organization or company. It is crucial to think about: who will have the ability to ask what kind of questions? Who has access to that? How are you seeing that evolve over time?

This goes back to thinking about the aim of the registry. What is the research question that underlies this? If you are thinking about making a registry to help support perhaps therapeutic development, then clinical outcome assessments and tying the types of queries that you are going to ask about those clinical outcome assessments may be very important because what you might be looking for is simple comparison data to see how this natural cause of the disease, the natural history of the disease, may eventually compare against when you have a new treatment that you have developed. Therefore, I think the starting point of thinking about querying begin by having a good understanding of the research questions that underlie the registry, then thinking about the data governance model and who has access to it.

“The starting point of thinking about querying begin by having a good understanding of the research questions that underlie the registry, then thinking about the data governance model and who has access to it.”

Lucia Monaco:

I would also take a step back and consider the very first step of collecting the data that requires the consent by the patient. That is another important issue, because patients in general are willing to share their data but collecting their consent also needs to be in a standardized and searchable way, so that the future use of the data that comes from their specific consent is made easier. This is something that has been addressed by several task forces that brought together the expertise of people from different countries and drafted a list of model consent clauses that represent a consensus of the key basic questions or items that should be included in a consent form, so that even registries that start with small patient associations do not have to start from scratch and already have a guideline that they can refer to. Making these clauses accessible and automatable so that they can be computer readable is also an important aspect that is being developed internationally.

“The very first step of collecting the data [...] requires the consent by the patient.”

Eric Sid:

When we were participating in that task force to model consent clauses, it was interesting for me to see that many of the questions about the types of research we may be moving towards in the future with are unknown: we are not even sure what type of research data we may be looking at in the future, video data, maybe even audio data, recorded data. There may be all sorts of information that we might want to be building these registries towards, and an important thing is that you may not know that at the starting point. Referring again to what Domenica was saying, really want to think about this in a modular way, you want to be thinking about how you can make this registry and add to it as you understand more and more about the disease and as your registry’s research questions mature. Being able to keep that in mind with the tools that you are using, these model consent clauses are great example of that because the language written in there was to design to help future-proof some of the research questions you may eventually ask.

“You want to think about [building a registry] in a modular way, you want to be thinking about how you can make this registry and add to it as you understand more and more about the disease and as your registry’s research questions mature.”

Domenica Taruscio:

In addition, what we suggest is to also use a dynamic consent, which means that you don’t need to update consent each time – it is dynamic. I totally agree with Lucia and Eric, but please keep in mind that you can also use dynamic consent, which allows you to continue your research, following the ELSI, ethical and privacy rules.

Sean Sanders:

I am thinking there must also be additional challenges when you are collecting consent and data from people across the world, and perhaps in countries where there are people coming from a rural community, it needs to be in a language that might be only spoken by a small group of people. Any thoughts from the group on that and how we can address that?

Domenica Taruscio:

Consent is a huge chapter, we could dedicate another entire future session on the matter, because it is not only an important topic for the indigenous population, but also, for example, for children, for disabled people... There are several rules we should be aware of and we should follow, to keep the patients, children, adults and disabled people safe.

Peter Robinson:

One thing that is very important in an international context is that different patients have different experiences with consent. Some patients don’t even know it. My experience as a rare disease doctor is that some patients, when you start to explain, they say, “Oh, stop, you decide for me.” That is a big temptation as a doctor, but it wouldn’t be ethical just to say, “Okay, yeah, we will do it.” Especially when we are extending these resources to parts of the world that have less experience with genomic research, it is important to understand that culture and to educate patients accordingly.

Lucia Monaco:

To add to this ELSI topic, data privacy is very important, and it can get very complicated, because data collected in different countries or continents respond to different legislations. Finding ways to preserve the privacy of patients, in a way that keeps data meaningful and useful, and that can bring back a return to the patient without disclosing the patient’s identity is a big technical, legal and ethical issue that is being addressed in several contexts.

“Data privacy is very important, and it can get very complicated, because data collected in different countries or continents respond to different legislations.”

Eric Sid:

I just wanted to add two ways in which patient organizations might think about how they can get involved in this process and really contribute. One is with patient navigators, who can sometimes help bridge the gap. Oftentimes when you are talking about many of these research questions, the language used may be very confusing for a patient. It may take a lot of time to go through and get the specificity required for an answer. So patient navigators that can help with understanding health literacy concerns that patients may have in terms of understanding the questions. Peter can easily talk about many of the different synonyms that might

go into describing a symptom: having someone to help navigate that language is important.

Another issue is also to think about the burden of going through and filling out the information itself. I have seen some registries that have extended well beyond several hours, with almost 200 different questions. Practicality-wise, you may be talking about diseases where fatigue is a symptom of the disorder. Having patients that could provide some perspective on the most value-added questions to ask and the length of the survey instruments being used in the registry so that they can understand the practicality of this, and the burden being placed upon patients in being able to participate in a registry.

Sean Sanders:

There has been some great successes and a lot of advancement in many of these types of registries. Where do we go next? How can some of these successes be applied globally to internationalize these registries more effectively?

Lucia Monaco:

Well, this is a great point, and it represents the effort of many organizations. Rare Diseases International set up an initiative to create a network of clinical resources that could be shared with different top tiers or levels of granularity across countries, continents and across the whole globe. That is an attempt to create a network that encompasses all the countries so that those clinical resources, knowledge centers are known, visible, linked and can be used by everybody as much as possible.

Peter Robinson:

In the nearly 30 years I have been involved in genetics and now bioinformatics research, things have changed enormously. Back in the 1990s, nobody was really thinking about standards. Well, that is a slight exaggeration, but now I would say everybody in the field understands the importance of standards, and many of the organizations internationally are now in the process of adopting standards. We are not quite there yet, but I would say everybody in the field knows that this is necessary. The main difficulties are with funding, so there is not enough NIH funding or research funding in general for groups to make and adopt standards. It is not something that you can do in a weekend. This requires a lot of software engineering and development. But I am overall very optimistic that the situation will continue to improve in the next 10 years.

Sean Sanders:

Thank you, Peter. We didn't even touch on funding, I think that would be a whole other webinar in itself.

Domenica Taruscio:

I hope that in the next two, three, five years, we can benefit from research in computing, for example. My worry is that we now know how to do make these registries, we know how to standardize data, we know how to collect good data and quality data and so on, nevertheless, we did not make the jump, we are still linked to traditional data collection.

I think that we need something more if we want to win the challenges linked to rare diseases. I don't know how or when, but I do hope that through machines and computers, we can improve these studies. Peter knows very well because he is the father of HPO : we can use HPO, we can communicate, data are interoperable, but nevertheless, it is time and resources consuming. I do hope that research in general, in other fields, not only medicine or biology, but also engineering and informatics, can help us to jump and go faster in research.

Eric Sid:

I will just piggyback what both Domenica and Peter said. You have data quality, you must have data standards, and then next, you need to think about data sharing. It doesn't help us if you have the quality and standards if others aren't able to potentially access it. As Peter was saying, if you have a rare disease, the problem in rare disease is really a problem of numbers. We need enough numbers; we need enough access to those different data from many different participants to be able to then create the type of statistical power we need to ask the research questions that we are looking for from these registries. Being able to create models towards data sharing and being able to make sure that the type of data that we are working in is open, not proprietary, are incredibly fundamental concepts that need to happen more for us to be able to ask more questions within the rare disease research space.

Sean Sanders:

I would love to extend our discussion further, but unfortunately, we are out of time, so we will have to end our conversation there. A huge thank you to all our panelists for providing their thoughts on this important subject.

The profoundly personal side of rare disease: Humanizing the therapeutic journey of patients

Medical systems around the world are at capacity. Patients frequently complain that their doctors spend insufficient time with them to really understand their ailments. Furthermore, doctors are hesitant to admit that they do not know a patient's diagnosis. Time constraints and financial pressures push doctors to make quick diagnoses and get the patient out the door. For patients with rare diseases, the situation is even more trying. The average delay for a patient to receive a diagnosis is 5 to 7 years, during which time they will have seen an average of over seven different doctors. Often forgotten are the humanistic burdens of the diagnostic odyssey. Imagine not being able to find the cause of your child's suffering for years on end. Imagine the stress, the pain, the frustration, and a growing sense of hopelessness in the wake of that suffering. In addition, the psychological burden for the patient and caregivers is huge, affecting their emotional and mental well-being, which in turn impacts their ability to properly care for their loved one. Add to this the financial burden that can be accrued by a family going from one health care provider to another seeking answers.

How best to support patients with a rare disease is ill-defined. Medical teams, especially doctors, are often insufficiently trained to explain to patients that they do not have the answers—or even know how to get them. Health care systems are not equipped to provide the psychological and social support patients need. Genetic counseling is complex in the setting of undiagnosed patients. Layered on this is the complexity of supporting the mental or physical disabilities that many patients with a rare disease must manage, whether they have a diagnosis or not. The humanistic support of patients with rare diseases and their families needs to improve. In this webinar, we'll meet experts who struggle with these issues and can help guide us on how to do better.

Panelists



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Alanna Yee
Encephalitis411,
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Sean Sanders, Ph.D.
Science/AAAS, Washington, DC
Moderator

The Conversation

Sean Sanders:

Hello and thank you for joining this 6th and final webinar in our 2022 "Science and Life" series on Rare Diseases, entitled The profoundly personal side of rare disease: Humanizing the therapeutic journey of patients.

Kathleen Bogart:

Thank you so much again for having me. I am a big fan of this series of webinars, so it is so exciting to be back. My background is that I was born with Moebius syndrome, which is a rare neurological disorder resulting in facial paralysis and impaired lateral eye movement. My experience growing up with a rare disorder that affected my communication made me fascinated with communication and with psychology. I therefore pursued graduate work, and I am now an Associate Professor of Psychology at Oregon State University, where I teach and study about these very issues. I study psychosocial issues surrounding rare diseases, disability, and ableism. A lot of my research has focused on the role of social support and stigma in the lives of people with rare disorders. I am also involved in rare disease and disability advocacy. I serve on the Moebius Syndrome Foundation Scientific Advisory Board and the American Psychological Association Committee on Disability Issues and Psychology. I am passionate about communicating about disability and rare disease issues to the public, like here, and in my Psychology Today blog.

Alana Yee:

It is a pleasure to be here today. I am a young adult who, for the past eight years, has been impacted by a rare neurological condition called autoimmune encephalitis. I have experienced many sides of the diagnostic and therapeutic journey. Before I got sick, I had worked in hospital labs performing diagnostic investigations. After I got sick, I spent five years undiagnosed while suffering from dementia-like symptoms. Now, after getting into remission as a result of seeking treatment in both Canada and the United States, I have become very involved in patient advocacy. I currently serve as the program director for the non-profit Encephalitis 411.

Amrit Ray:

It is a real pleasure to be here. I am a big fan of this series and honored to be a part of the dialogue. My background is that, personally, I am a rare disease advocate and a rare parent. Professionally, I am a physician researcher. I have been involved in the biopharmaceutical industry the last couple of decades and had some executive roles relating to overseeing research access and advocating for policy changes. I am very interested in looking at a bioethical perspective and some of the ethical aspects that surround rare disease. I wear a few different hats, so

today I am here to share my personal views and not representing any organization. I am very happy to participate with such an esteemed panel.

Sean Sanders:

Quite early on in this series, one of the panelists said that collectively, rare diseases are not rare. The name is a bit of a misnomer. The diseases on an individual level are rare, but there are millions of people around the world who are suffering from these rare diseases. Amrit, how do you think about this fact, in a world where so much attention goes to well-known diseases like heart disease and certain cancers? What is your perspective both as a rare parent and as someone in the biopharmaceutical space?

Amrit Ray:

I think this is something that really merits discussion because it is a surprise for many people to know that what may be individually rare is collectively common. I can start with giving you the perspective from the United States and then expand to perspectives from elsewhere, or areas where I have had the opportunity to work around the world, which have been inevitably eye-opening. In the United States, there are about 30 million Americans who are diagnosed as having a rare disease and who are considered as having a rare disease (diagnosis is a separate question). 30 million is almost like one in 10. Then, you start thinking through the family members, the social contact of those one in 10... I imagine that every single person listening to this webinar is probably in touch with someone with rare diseases. If you look at Europe, you find very similar numbers: about 30 million Europeans are estimated to be living with a rare disease. Regarding Asia, I have had the chance to work in China a lot recently, and the Chinese Government has recently been putting out new definitions and a list of more than 120 rare diseases in the last couple of years. The numbers are quite staggering, in terms of "rare" and the surprise is that it is actually not rare.

Beyond just the numbers, statistics, epidemiology and population, we should also look at the individual, human level: the level of suffering, the impact on broader life. Stepping back, I think it is very natural to look at the personal level: the impact on life is so wide. I know some of my fellow panelists are going to speak of that.

From a societal level, there is a very significant impact. The economic burden study in the United States was recently published. It estimates the burden of rare disease, meaning not just the immediate medical cost, but also including the broader, sometimes harder to measure, indirect costs, such as the impact on families and so forth. The number is quite staggering: it exceeded a trillion dollars per year for the United States. That study only actually looked at a small subset of little bit under 400 out of more than 7,000 rare diseases. So, it is probably an underestimate. To put that into context, it was estimated that that similar total cost for diabetes was about \$327 billion a couple of years ago. It is sometimes eye-opening to see how impactful it is at the human and societal level around the world.

"The economic burden study in the United States was recently published. It estimates that the burden of rare disease, meaning not just the immediate medical cost, but also including the broader, sometimes harder to measure, indirect costs, exceeded a trillion dollars per year for the United States."

Sean Sanders:

There are many rare diseases that we don't know about. We might have friends, even family members who might have a rare disease that we just don't know about - we don't even realize that impact. Kathleen, you have mentioned before that you have a rare disease that is obvious - it is not something that can be hidden. But there are many people that have a hidden rare disease. What are your thoughts on that?

Kathleen Bogart:

I think that it is an important distinction. Some rare diseases are apparent and some are invisible or hidden. It is much more likely that people have a hidden rare disease. There are challenges on both sides of that spectrum. One of the challenges that people with invisible rare diseases experience is getting a diagnosis. Research shows that those with invisible conditions are less likely to be believed by their friends and family members and even, in some instances, by doctors. That can lead to an even greater diagnostic delay. Some of the research that we have done shows that there is an average of seven-to-nine-year diagnostic delay in America, and we think some of those people with invisible conditions are especially likely to experience challenges with that.

Those with apparent disorders, like me, have a different set of challenges. I have a disorder that is readily apparent. I like to call Moebius syndrome "highly visible but unrecognizable", because there is so little general awareness about facial paralysis or Moebius syndrome, that I might walk into a room and people would notice that I look different. However, they might struggle to put their finger on why and make all sorts of misinterpretations. We find this happens with all sorts of facial paralysis disorders, most of which are rare. We may be mischaracterized as simply being unfriendly or being unintelligent. You can see how that might be multiplied by the thousands of types of rare disease out there. So yes, there really are some specific psychosocial challenges depending on whether a condition is rare or common.

Alana Yee:

Picking up on the theme of diagnostic delay: living with no diagnosis is like wandering through a perpetual fog. While dealing with the grief and logistical nightmare of being forced to make adjustments to your lifestyle, your aspirations, your career plans, you are facing an undefined, nameless monster. You don't know how big the monster is, which direction it is coming from, whether it will come in with a lethal hit, and where its vulnerabilities are. Being on that journey, in the fog, leaves you with a sense of

fear and uncertainty that can make it seem impossible to move forward in any meaningful way. As an example, in my patient journey, I had been a previously healthy young adult aiming for a career in academia, when I had a flu like illness that left me with significant memory problems. I went to my doctor, and I went to some specialists and got some diagnostic investigations done, and nothing came back abnormal. Meanwhile, I continued to deteriorate and suffer from globalized cognitive decline – not just the memory problems, but also issues with verbal fluency, executive dysfunction, slow processing speed... That was to the extent that I had to leave university altogether. There I was, experiencing this profound debilitation. Meanwhile, I didn't have any objective evidence to validate my experience. In this scenario, I think what tends to happen for rare disease patients is that their experience is dismissed and psychologized. They may receive a diagnosis of depression or anxiety, which can act as a red herring in medical records and distract from the search for the primary cause of symptoms. Ultimately, the patient is kind of just left in this position where they are expected to move on and learn to power through things.

Amrit Ray:

Alana, I really appreciate your courage in sharing that. Even as a physician, when I was advocating for my daughter with a rare disease and first became familiar with the term “diagnostic odyssey”, it really didn't sink in until I looked at the numbers. On average, patients who are diagnosed in the United States with a rare disease must go through 17 different health care professionals before they get a diagnosis. There certainly is a delay, but I think we can all empathize with how difficult it is to reexplain yourself and to be referred from one place to the next. Frankly, 17 is too many.

Sean Sanders:

Alana, when you started going through this journey, how did you talk to people around you such as your friends and your family? It must have been very confusing to you, as you didn't know what was going on with yourself but you knew that something was wrong without having any objective evidence. I think that could be very helpful for others who are may be going through a similar journey.

Alana Yee:

Candidly, there was a lot of despair and social isolation because you are essentially living in a reality that the medical system is not acknowledging, and you can sometimes grapple with the question of, are your symptoms real, or are they psychosomatic? It becomes very easy for others, friends, spouses, and employers, to disregard the very real day-to-day challenges you face if you have no name for the cause of your suffering. In concrete terms, for me, it was very shocking and devastating to lose my cognitive capacity and be medically gaslit by some doctors into believing nothing was medically wrong, and to be expected to plan for the future and take care of myself when I had no idea what tomorrow would bring. I never anticipated that the monster would only grow bigger and slowly disabled me over five years until I was catatonic.

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Sean Sanders:

It is amazing. To echo what Amrit said, I very much appreciate you sharing your personal story. I am sure it isn't easy. Amrit, do we see a difference in the diagnosis of men versus women with these rare diseases that are not obvious or not apparent? I ask this question because I have seen evidence that women tend to be believed less than men when they talk about a symptom that is not obvious. They are more often told that it is psychological issue rather than a real medical issue.

Amrit Ray:

I don't know the answer to that, Sean. I don't know if there are studies or evidence to show that. I have a few broader reflections on diagnosis but maybe, Alana, would like to comment on that?

Kathleen Bogart:

We have done qualitative research on women with rare diseases, and they do share a lot of these same experiences that Alana was talking about, of being medically gaslit. I just wanted to say, Alana, that that story is horrifying, and also compelling, right? Thank you so much for sharing it. I think, sadly, it is not that uncommon for women to experience something like you did. I am really glad that we are having conversations like this to raise awareness about it.

Amrit Ray:

Yes, I echo that. I really appreciate the courage in sharing that because I think that will impact many others when they hear the story. One thing, I would just put as a perspective to consider as well, is that the majority of patients with rare diseases, about 70% of them, are diagnosed in children. Children, of course, are not in a position to advocate for themselves. So, they are voiceless in many ways. Considering this fact, and going back to the very difficult Odyssey we talked about: right now, in the United States, there have been a lot of efforts placed on expanding newborn screening, to start right at the beginning. There are about 12,000 babies born in the United States every year with a treatable condition.

However, the screening that takes place is unfortunately quite inconsistent around the country. It varies from state to state. There is a uniform screening panel that is recommended, the RUSP. However, even though we know that there is a finite list of diseases and that we can still expand the list of diseases, today, that recommended panel is not used in all states. In fact, it is not used in more than half of the US states. So, I think, in many senses, we are giving up an opportunity there. We are giving up a

chance to help children that is in our hands. I think all of us, could probably say that a baby's life shouldn't depend on what zip code they are born in.

Sean Sanders:

I appreciate you bringing it up. We did a webinar, I believe it was last year, on some of the challenges with prenatal and neonatal screening, and how it differs, like you said, across the US, and of course, around the world, where some countries are much better than others, and some countries have no screening for obvious reasons. Kathleen, in a very practical sense, how does the classification of a patient's condition as a rare disease impact the care that they might receive?

Kathleen Bogart:

Well, there is good and bad. Having a rare disease, of course, means that, as we have already discussed, it is more likely that we experience diagnostic delay or may go on for years without a diagnosis all together. That is very challenging. The plus side, at least if we are talking about certain countries like America, is that there are some policies that actually protect people with rare diseases. For example, here, in America, the Orphan Drug Act was actually created many years ago through lobbyists to ensure that people with rare diseases are being offered drugs, and that drugs are being developed for this group of people. This would perhaps not occur otherwise, because there would be a perception that the audience for this drug would be too small to make it financially feasible. So, policies like this ensure that people with rare diseases are prioritized in medical research, at least to some extent. Of course, the great thing is that it is not just people with rare diseases who benefit. A lot of times, these medical and drug breakthroughs that are made because of these policies, end up benefiting people with many diseases, common or rare.

"Policies like [the Orphan Drug Act] ensure that people with rare diseases are prioritized in medical research, at least to some extent."

There is another very tangible thing that I can talk about from my own experience. Being a person who has a disease that affects only 2 to 20 in a million people, it means that I would never encounter someone with Moebius syndrome in my everyday community. Lots of common diseases come with support groups at their local community center or hospital. I did not meet anyone with Moebius syndrome until I was in my mid-20s. To do that, I had to travel across the country to a conference for people with Moebius syndrome. I fell in love with the experience of being a majority group number for the first time in my life. Being surrounded by other people who looked like me and not having to explain. So, I got very involved in that organization, I haven't missed a conference since. I think the opportunity to connect with other people, while quite rare when you have a rare disorder, can be really valuable.

Amrit Ray:

That is a great point, Kathleen. I think one of the positive things, that I have re-experienced in the rare community is the coming together of patient organizations and the willingness of patient organizations to be very welcoming, very inclusive, but also very generous in sharing their experiences, their learnings, their insights, so that, as a total community, we can hopefully bring more impact and advocate more strongly. I have the honor of serving on the board of the EveryLife Foundation for Rare Diseases, who is very involved in policy making. I have had the opportunity to partner with many dozens of organizations for individual rare diseases. Europe has EURORDIS... Organizations spring up around the world, which I take as a very positive step because of this need to increase awareness, increase education, and increase what I like to call health literacy.

Sean Sanders:

Alana, I understand that you finally got a diagnosis for your rare disorder. You are now in that group of somebody who has been classified with a rare disease. Could you please tell us about the mental and emotional journey that you had before you had your diagnosis and then after having it? What changed (if anything changed for you)? Did it help at all in moving forward in your life with a rare disease?

Alana Yee:

Yes, it helped immensely to be able to connect with a patient community and to understand that I wasn't alone in dealing with my issues... and that my illness, though it is rare, it is not as rare as I was originally led to believe. Being able to connect with a patient community really helped to open my eyes to the power of self-advocacy. I wouldn't be alive today if it were not for getting onto Facebook groups and other online forums, and asking fellow patients questions about how to navigate the medical system, to receive practical medical tips from them, and equipping myself with knowledge so that I could ask better questions to my doctors and have more productive conversations with them. That said, it did take me years to understand the true power of self-advocacy, and that was also with having prior exposure to the medical system.

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I think there can be a lot of value to broader society in perhaps reframing the role of doctors and patients in medical care, which is something that came out of my conversations when connecting

with fellow patients and caregivers. The average doctor can do more to demonstrate respect for the patient voice, encourage patients to seek out more reliable information and connect with patient support groups and see patients as meaningful collaborators in their care. The average patient can also do more to recognize the value in seeking out reliable information, empowering themselves, and stepping into a more active role in their care. It is not to place blame on other side for struggling to manage a rare disease, it is simply to draw awareness to the fact that patient support groups and patient advocacy brings a very valuable lens to the table.

Sean Sanders:

Wonderful, thank you. Amrit, may I ask what is your experience on this topic, from the perspective of a parent? What did you go through with your daughter in that diagnostic odyssey? What impact did it have on your family and your relationship with your daughter?

Amrit Ray:

Thank you, Sean. First of all, I empathize with Alana. It means a lot to meet others and to join the community, and it is not easy to do that. I found that there were a couple of things that really stood out to me. Firstly, there is an inevitable process of education, that certainly begins with self-education, and also, many times, being an advocate to educate your carer, your physician or nurse or whoever it may be. Typically, what happens is that you are first dealing with generalists, and then specialists, and then subspecialists and super specialists. By the time you are many steps down the chain, the education need can certainly have gone down on the technical and medical aspects. But your education need remains on the human aspects. In my case, the human aspects were, for example: what is the impact of the rare disease on schooling? What is the impact of the rare disease on the ability to play with other children? What is the impact of the rare disease on the practicalities of parenting? What are the costs associated with that? Those types of things, I think, still require a great deal of education, conversation, and dialogue.

Secondly, it is actually interesting, Alana, to hear you mention Facebook groups. This is because, of course, 20 years ago, probably no one had Facebook groups. Social media is actually a tremendously positive opportunity and a positive channel. Putting on a slightly different hat now, as a researcher and educator, what I have always been struck by is that if you look at health literacy in general, not even for rare diseases – so, the ability to obtain and use health information - it is usually down in the single digits in most countries around the world. I can only imagine that it is worse for rare diseases. Where reading literacy is often up near a hundred percent, health literacy is down in these single digits. In the United States, it is about 12% according to CMS, meaning that only one in 10 Americans would be considered proficiently health literate. That is a very difficult number, and I think all of us have a role to play in lifting that number.

Picking up on Alana's point, what is interesting is that social media and digital literacy, is highly penetrating. So, digital literacy

is typically up near a hundred percent. In some countries in the world, it is even more than a hundred percent because people have multiple phones or multiple sim cards. I think that presents us with an opportunity. One thing that struck me is that, as we all react to different channels, if you take all of Facebook encounters, all of Instagram encounters and all of Twitter encounters, one channel, TikTok, exceeds them all today. In a sense, that is an opportunity for us to be sensitive and aware of, as a mechanism to increase health literacy. I think the future is going to be digital health literacy.

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Alana Yee:

For me, being able to connect with others online has been huge in my journey. Doctors understandably don't have the time to scour the latest medical journals and connect with patient organizations or attend conferences. Sometimes, patients are the ones that are better positioned to do this. They become experts in their illness in their own right. They have the lived experience, they get resourceful, they connect with others online, they go into PubMed and try to find those medical journals to answer the questions or the problems they are trying to solve. They do their own research. I think that is something that can tend to be underappreciated in the average patient-doctor relationship today.

Kathleen Bogart:

I completely agree with these points. I just want to emphasize how helpful connecting with others online has been for me as well, in terms of becoming more expert in my own disorder and getting to know other people. As I mentioned, I would either have to travel across the country or across the world to meet others. As the internet has opened up, it means that I am able to connect with people across the world very easily. I can see a major change in my own lifetime. Of course, as Amrit said, I was born with my rare disease, so I was a child with a rare disease, and it was my parents who needed to go through that diagnostic odyssey and learn about the condition.

“I just want to emphasize how helpful connecting with others online has been for me as well, in terms of becoming more expert in my own disorder and getting to know other people.”

It took two years for them to get a diagnosis for me. That was at the time when people did not have regular access to the internet, so they really struggled. In many ways, they were privileged that they had high health literacy and some access to medical journals and things like that. I think now about how much easier that

journey would have been if they had access to connecting with other parents. I can see in Facebook groups now, there are often parents who are joining and saying, “We think our child has this diagnosis” or “We were just diagnosed”, and getting immediate support and information from others... It is so lovely to see that change happen in my own lifetime. Also, it makes me think about how thankful I am that my parents persevered with fewer resources than that domain than there are now.

Alana Yee:

Another angle to look at this is: even if you are not coming up with answers or finding solutions to your immediate medical issues, doctors can still provide a lot of benefit in simply seeing the patient as a full-fledged human being and not just a set of flat values. There is a lot of value in acknowledging their suffering and being open about saying “I don’t know”, or just engaging in meaningful dialogue, or respecting a patient’s choice to keep pursuing answers elsewhere. That approach from doctors was so powerful, and it helps to inspire a sense of confidence, resilience, hope, and grit, which can act as a shield against just succumbing to despair, waving the white flag and losing the will to live. So, even if the doctors feel like they can’t necessarily do anything concretely for the patient, actually remembering that human component to the patient interaction is huge.

Sean Sanders:

It is clearly important that we need to bring together communities, people who are medically literate, who know about rare disease and the patients who are experiencing these rare diseases. One of the things that has come out of our previous webinars is this has to be an international endeavor, because as Kathleen was saying, there is only a few people in a million who might suffer from Moebius syndrome. We need to have access to the worldwide community to pull together all those people. Amrit, do you have any thoughts on how to do this? How do we reach across the world to share information and expertise? How do we leverage technologies such as social media to do this?

Amrit Ray:

It is a very important question. I think what you are pointing to is shifting gear from diagnosis and understanding to reach for solutions. In reaching for those solutions, there are a few dilemmas. A few of the challenges are always going to be related to the very small numbers of individuals with these diseases (reflecting on the numbers Kathleen was sharing about Moebius). I think many rare diseases individually have very small numbers. As a result of that, it can often be quite difficult to do research within one locality or one country.

So, the opportunities there are multifold. There are sometimes opportunities to bring together information from across different countries and different communities. There are opportunities to put together registries that allow us to study diseases in a methodical way over time, opportunities to use real world

evidence. Sometimes, a lot of clinical studies look at using controls, but when the numbers are very small, it can be very difficult to find controls. At a delay level, it is easy to understand that if you have a lot of data, that could give you a sense of what a control may look like, a synthetic control. So, there is a lot of positive reasons to be collecting and sharing data internationally.

That is one thing. The second thing I would point to is that, in terms of policies, it is very important to encourage the researches undertaken in rare diseases. If you look at very small numbers, the incentive for researchers, for a private enterprise, to invest in research can be very challenging, and particularly for public companies as they have to think through many considerations. If there are policies in place that encourage and stimulate research, encourage collaboration, and encourage methodologies, that often gives us some of the way forward. Kathleen was mentioning the Orphan Drug Act, and I think that was a wonderful step, but there have also been many positive steps subsequent to that. I think encouraging those steps of policy and regulation internationally, would also be a positive step.

Kathleen Bogart:

I completely agree with everything you said, Amrit. You are discussing the power of the collective, looking internationally because we are dealing with these really small numbers. One thing that I often think about is the power of psychosocial research and psychosocial treatment for people who are experiencing a variety of rare disorders. I want to speak for a second to what Alana has said about being psychologized and medically gaslit. This is not of course what I am talking about here. Rare diseases are real, and people deserve to be believed. However, the struggle at all parts of that journey is also real. There is a lot of uncertainty. It can feel very isolating. People need psychosocial support all along the way. I strongly believe that we can do a lot better in supporting people by looking across rare diseases and internationally, looking at psychological things that we can do, interventions.

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My research has found a lot of commonalities across very different biological disease processes. The psychological challenges that we have all been talking about today are quite similar, right? We are talking about stigma, we are talking about social isolation, we are talking about stress and uncertainty. There are many well developed psychological interventions, such as Acceptance and Commitment Therapy, or Cognitive Behavioral Therapy, that have not yet been applied to rare diseases. Relatedly, psychologists have not been appropriately trained in rare disease issues, and honestly, in disability issues at large. This is something we are

working on with the American Psychological Association.

I see this as being twofold. First, I think we need to fund better international cross rare disease research on psychosocial support. Second, I think we need to train our mental health care practitioners about the specific challenges of rare diseases. So, I think that could make a huge difference for people at any point in their diagnostic odyssey from searching for diagnosis, to living long term with their condition.

Alana Yee:

Kathleen, you brought up several great points there. I think the value of patient organizations can tend to be overlooked in advancing the field of rare disease. Tactically, they can play a unique role in aggregating patients together, and helping in research recruitment, they can concentrate knowledge from the lived experience, and they can pick up on patterns amongst their patient population in a way that an individual expert simply can't, due to the rarity of rare diseases. I will give you some personal commentary from the encephalitis field. Encephalitis can present in a number of ways, but textbook autoimmune encephalitis presents very dramatically, with neuropsychiatric symptoms such as seizures, psychosis, and cognitive decline. It is very alarming. Some patients require ICU admission, and in some cases, it is fatal. Current treatment guidelines have developed in such a way to essentially optimize for getting the patient out of the hospital. From the medical side, the benchmark for successful treatment is essentially whether the patient can walk and talk after the onset of their illness.

However, patients are often left with invisible symptoms of an acquired brain injury that are overlooked. Thanks to patients raising their voices and patient support groups, researchers are now starting to ask the question: what outcomes actually matter to patients? Sure, they can walk and talk, but many are left with debilitating persistent fatigue and cognitive impairment that prevents them from returning to school or employment. If these were considered earlier on in the development of the encephalitis field, best practices for treatment would be more advanced by now, because we would be optimizing for the outcome measures that matter most to patients. That is just one example of how greater patient consultation and greater regard for the patient voice can ensure that limited research dollars and the development of the field remain patient centered and focused on the things that patients actually value.

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Amrit Ray:

Yes, Alana, I would align 100% with you on that. I think you have made some very good points. Similarly, Kathleen, I think you

make some very important points about providing the appropriate psychosocial support and frameworks. It is interesting, reflecting on how many opportunities we have seen now, we are seeing right now some tremendous leaps in science, with technologies that, when most of us were born, we wouldn't have just ever thought imaginable, such as gene therapies and many other quite incredible steps already happening.

I think the realization is that it is not science alone, but it is very active involvement of the patient community in some of the regulatory steps. For example, Patient Focused Drug Development efforts, PFDD efforts, and others, have really highlighted insights. I remember a patient one time who shared with me: “I see all my lab results, and I see all of my metrics that are in my medical charts, but I want you to really understand what matters to me most is the ability for me to go skiing. That is what brings me happiness, that is what brings me joy. That is what matters most in my life. So, if there is some combination of these medical metrics that can allow me to do what I enjoy, I just want you to understand that that is what would change my life.”

That is one human example, that probably put some color around the idea that there has to be very active dialogue with patients, not just with their carers, but also with regulators, with biopharmaceutical companies, and many others, so that patients are followed in throughout the process. There can be a bit of humility and understanding. What it is that is most important to patients?

Sean Sanders:

Thank you all for sharing those wonderful points. One of the aims of this webinar series is to talk to a very general audience, not necessarily just patients and the families of patients of rare diseases. Kathleen, what should the general public know about rare diseases so that they can become better advocates?

Kathleen Bogart:

I love this question. First of all, we can reiterate that rare diseases are common: one in 10 Americans will have a rare disease. So, we need to be aware that they exist, that there are challenges around accessing diagnosis, there are challenges around accessing treatment, and that policies that help further those treatments, like Amrit was talking about, can benefit everyone. Also, we need to be aware that rare disease touches everyone. I can share some insights from my own experience. I have been teaching at Oregon State University for 10 years now. My classes often involve talking about disability and rare disease. Over the course of that time, I have had many wonderful students who sometimes circle back to me after a few years.

It is my favorite thing when they say, “Oh, I remember that one thing that you said, and it actually mattered in the real world”. I have had three different students or collaborators who at that time did not have a rare disease diagnosis, then circled back years later and say, “I was just diagnosed with a rare disorder, and I feel so prepared, because we spent all this time thinking about the way people can navigate rare disorders”.

Alana, we also spent a lot of time talking about patient advocacy and patient empowerment, so they always say, “Well, the first thing I did was I looked for the Patient Advocacy Organization”, and so it is really amazing. I am sure that there are more than three people to whom this has happened and to whom this will happen. That just shows that rare disease needs to be part of our everyday conversations so that people can be aware that they can and will happen to everyone. It will happen to their families; it might happen to themselves. It is important so they know where to go and what to do, so they don’t feel alone.

Alana Yee:

I think the notion of rare disease can sometimes tend to engender a sort of, “shrug your shoulders” type of response, and come with a defeatist attitude of just bluntly, “too bad, so sad, that is just going to be the reality for the patient now, and this is going to be their fate”. I think there needs to be more of a narrative shift in our culture, that it does impact more people than you think. It is not some obscure thing that you can just put in a box and forget about and pretend it won’t ever impact you. Additionally, some are highly treatable, and many people still have a tremendous quality of life, especially if provided with connection, support and if they experience compassion and empathy from their community members.

“There needs to be more of a narrative shift in our culture, that it does impact more people than you think. It is not some obscure thing that you can just put in a box and forget about and pretend it won’t ever impact you.”

Amrit Ray:

I fully agree Alana and Kathleen with all of these points. I think that one of the things that always strikes me is that understanding is a very important door opener to allow people to care and, in a sense, anything that we can do to increase understanding. This webinar is a very good step, and there are many others. Anything that we can do to increase understanding at a very human level is important. The numbers we talked about are staggering. But at the same time, I often think that even if there is just one patient, that doesn’t mean that you don’t have a right to get help or a right to receive care - the World Health Organization 80 years ago recognized health as a human right. One of the things we have to be doubly sensitive to is that when there are small numbers, those numbers can often mean that patients are vulnerable because they don’t have all the support mechanisms that would surround large diseases. If anything, there is a need to educate, but there is also a need to call out that there are some vulnerabilities here too.

Alana Yee:

Echoing what Amrit had said, there is a lot of value in recognizing rare disease patients as just fellow humans that want to be seen, heard, and validated. Recognizing that we still have hopes and aspirations that extend beyond managing our rare disease. An encouraging word of understanding and kindness goes a long way.

Sean Sanders:

I really like the idea of ending on a note of compassion and kindness. I think we need that in this world more than ever, and especially for those who are dealing with a rare disease and the challenges that they bring. Thank you very much to our amazing panel for being with us today, and for sharing not only their knowledge and their wisdom, but also their personal stories. I really appreciate that and I am sure our audience does as well.

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