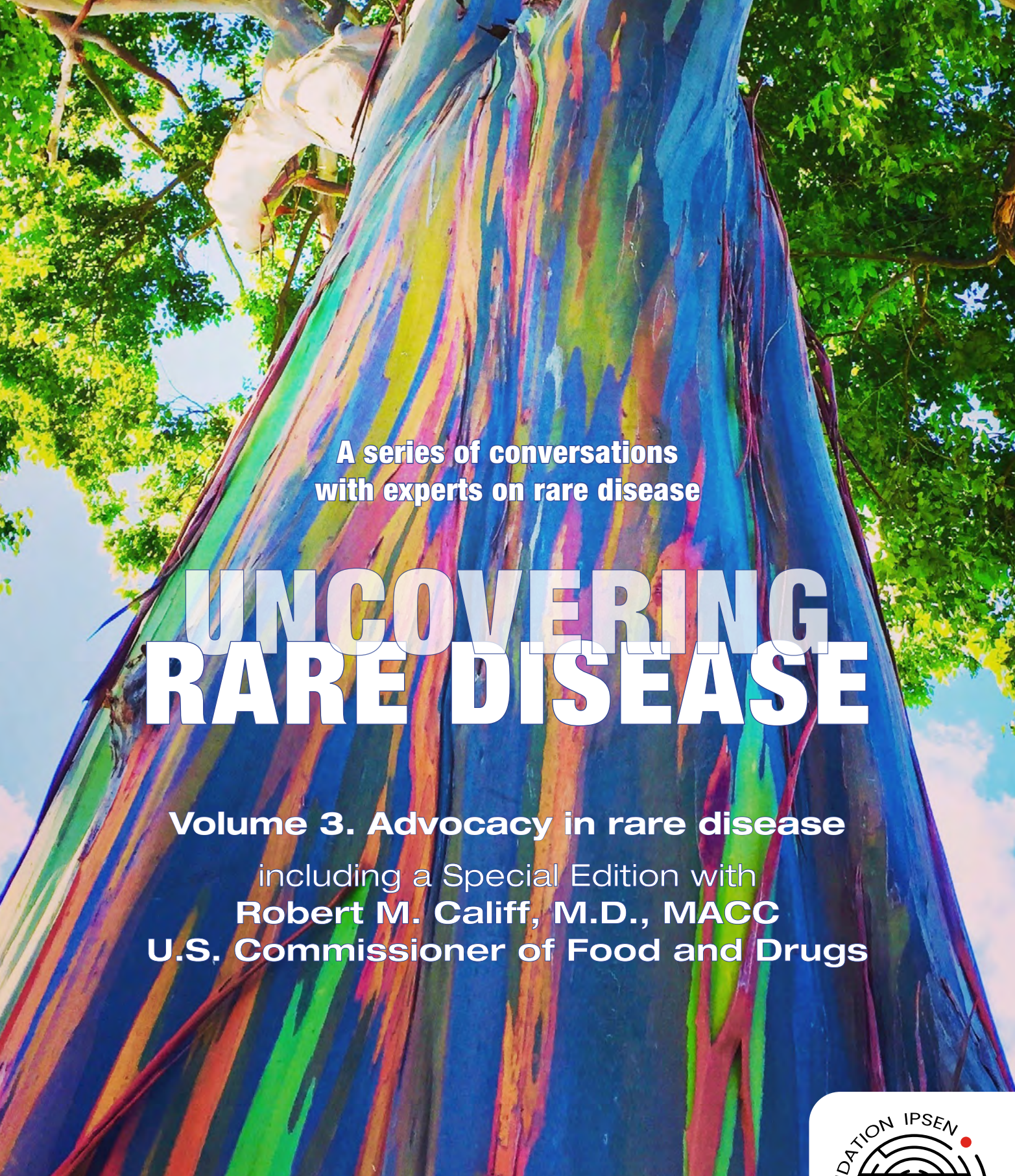

A series of conversations
with experts on rare disease

UNCOVERING RARE DISEASE

Volume 3. Advocacy in rare disease

including a Special Edition with
Robert M. Califf, M.D., MACC
U.S. Commissioner of Food and Drugs

Webinars produced in collaboration with

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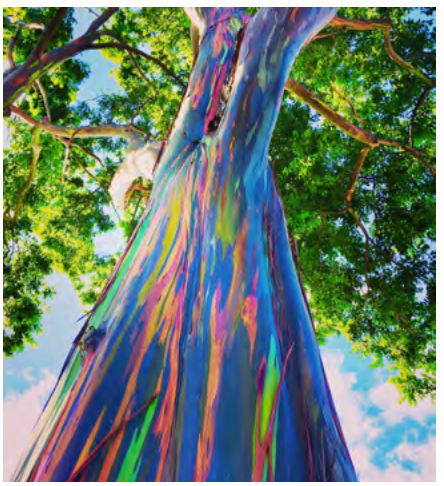

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Have your say!

Uncovering Rare Disease

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

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

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Special Edition: A Fireside Chat with the U.S. Commissioner of Food and Drugs

Science Webinars is pleased to welcome Robert M. Califf, Commissioner of Food and Drugs at the United States Food and Drug Administration (FDA), for a Fireside Chat about the intersection between the FDA and rare disease. This intimate and enlightening conversation will provide unique insights into the challenges and opportunities faced by individuals and organizations dedicated to advancing research and treatment options for rare diseases.

While each rare disease may affect only a small percentage of the population, collectively their impact is enormous, with more than 7,000 rare diseases affecting 1 in 10 people. Patients, families, caregivers, and advocacy groups work tirelessly to raise awareness, accelerate research, and navigate the complex regulatory landscape. In this Fireside Chat, we will explore how the FDA, as the regulatory authority for medical products in the United States, collaborates with these advocates to ensure timely and safe access to innovative therapies for rare disease patients.

Watching this Science Webinar, viewers will:

- Learn about the FDA's commitment to addressing rare diseases and how they incentivize the development of treatments
- Hear the Commissioner speak to FDA collaborations with international regulatory agencies, patient advocacy groups, and individuals with rare disease
- Explore recent technological advances that are streamlining the regulatory process.

Panelists

Robert M. Califf, M.D., MACC
Food and Drug Administration, Washington, DC
Robert M. Califf, M.D., is Commissioner of Food and Drugs, and head of the U.S. Food and Drug Administration.

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

The Conversation

Erika Berg (*host*):
Welcome to this special edition of our 2023 Science Series on Advocacy in Rare Disease, a fireside chat with the Commissioner of Food and Drugs. I am Erika Berg, Director and Senior Editor for Custom Publishing at Science, and I will be the moderator for this discussion. While each rare disease may affect only a small percentage of the population, collectively, their impact is enormous. More than 7,000 rare diseases affect one in 10 people. Patients, families, caregivers, and advocacy groups work tirelessly to raise awareness, accelerate research, and navigate the complex regulatory landscape. In this fireside chat, we will explore how the FDA as the regulatory authority for medical products in the United States collaborates with the rare disease community here and abroad to ensure timely and safe access to innovative therapies. Today I am pleased to welcome Dr. Robert M. Califf, Commissioner of Food and Drugs at the United States Food and Drug Administration for this chat about the intersection between the FDA and rare disease.

Robert M. Califf:
Thanks, Erika. It is good to be here with you. I am Commissioner of the FDA. As you noted this my second stint at the FDA; I was previously commissioner in 2016-2017. I am a cardiologist by training. I spent 35 years in busy clinical practice, but in the midst of that I was always fascinated by the fact that we did not have treatments for a lot of diseases, including common diseases and rare diseases. I got very involved in the development of new treatments that led to a lot of interactions with the FDA and finally ended up being asked to be commissioner twice now. There is a lot of work to do. It has been a fun career.

Erika Berg (*host*):
Thank you so much for being here today, Robert. My first question for today is: what is the FDA doing to prioritize rare diseases within its regulatory framework? In other words, how does the FDA juggle the needs of the few to the many?

Robert M. Califf:
It is a great question because many times in life we have to choose one or the other. But I feel like a real advantage that society has given the FDA is we do not have to choose rare diseases between the two. We exist in an environment of user fees where the companies that develop products pay into the FDA, which allows us to grow even at times when congress is not necessarily being generous with allocating money to the FDA. And so, of course,

common diseases are very important. They are the leading cause of death and disability, but the special suffering and difficulties of people with rare disease are critically important to the FDA. Over the last few years, we have gotten substantial funding to grow our capabilities and help to deal with rare disease, because this is where the science is so exciting now, and really explosive in terms of how new science could lead to treatment and cures for diseases that were completely unapproachable in the past.

"We exist in an environment of user fees where the companies that develop products pay into the FDA, which allows us to grow even at times when congress is not necessarily being generous with allocating money to the FDA. "

I brought a few notes here, just some of the evidence of what has gone on recently since the Orphan Drug Act, which was 40 years ago. There have been 600 new drugs with 1,200 indications. That is a lot. But we got 7,000 diseases, so it is only just a start. But just this year, just to give you the list, there is the first treatment for Friedreich's ataxia that is a rare inherited degenerative disease of the nervous system; it gives people difficulty walking and being coordinated. So, an enzyme replacement therapy there has great promise. There is the first treatment for adult and pediatric patients with CD55 deficient protein-losing enteropathy, and you begin to know by the names of these diseases, they are not common and they are very specific to the cause, but this is a big step forward.

"The special suffering and difficulties of people with rare disease are critically important to the FDA."

In 2022, 63% of the novel biologics that were approved were for rare diseases. There was the first gene therapy to treat wounds in patients with dystrophic epidermolysis bullosa, which is a rare disease that causes serious skin disorders. There was the first gene therapy for ambulatory pediatric patients ages four and five with Duchenne muscular dystrophy; that is a big one. There was the first gene therapy for adults with severe hemophilia. So, we are working hard on this. To a large extent the FDA are like referees. We do not develop drugs; companies develop drugs. The NIH and academia fund the research and do the research that leads to the later development by companies and we have the hard job of judging whether the evidence supports that these treatments should be allowed onto the market.

"In 2022, 63% of the novel biologics that were approved were for rare diseases."

Many of them are quite expensive. It is important that what patients are offered actually works, as opposed to people just promising that it may work. Our Center for Drugs has put together an accelerating rare disease cures program or an ARC program, which is really focused on educational workshops about how all this works. It is not a simple process. If you think about what it takes to develop a drug from a concept that needs to be translated into a therapeutic target and a drug that would hit that target and then not cause other unexpected toxicities due to hitting other targets at the same time. The only way to ever sort this out is through human clinical trials. It is a very high priority. We have to keep both of these areas in the forefront of our minds.

"Over the last few years, we have gotten substantial funding to grow our capabilities and help to deal with rare disease, because this is where the science is so exciting now, and really explosive in terms of how new science could lead to treatment and cures for diseases that were completely unapproachable in the past."

Erika Berg (*host*):
I am just curious about something you mentioned in your answer, that in recent years there was an increase in funding in this area. I was curious where did that funding come from and what changed?

Robert M. Califf:
I think the best way to think about this is in historical perspective. The NIH was funded generously by Congress for a number of years, particularly in the area of genetics; Francis Collins, the former NIH director, that was his big thing. I remember for about a decade afterwards, people said, "Where is the bee; we put all this money into it?" Now it is really paying off in that genetics and the byproducts downstream from genetics leads to concepts of therapeutics. Then companies started developing, and investment came in, and now we have this explosion of new potential therapies. But if we just kept the FDA with the same people at the same size, we couldn't handle this increase. The user fee program is a program where the industry says we need good and high numbers of people to evaluate our applications. That is actually where the funding came from. In the biologics area alone, over 100 people were added to the FDA last year, this year, and next year to handle what we expect will be a great increase in the number of new therapies. This is good news for people with rare disease.

Erika Berg (*host*):
How is the FDA incentivizing the development of treatments for rare diseases considering the limited market potential for such therapies?

Robert M. Califf:
We all recognize the difficulty that first of all, just the cost of development is great because you have to put all the care and quality into the development of a drug for rare disease as you do for

a common disease where there may be a huge population that would then use the drug. The economics are going to be better to start with in common disease, and you have to find people to participate in the clinical trials that are needed to be sure that you are helping people and not hurting people with the treatment. Societal interest in this 40 years ago got to the point the Orphan Drug Act was passed by Congress. It puts into place a number of incentives for the industry, both tax incentives and special situations, some funding for research funded by the FDA. It is one of the few areas where FDA actually has money from Congress to fund research about the natural history, because in many cases, you cannot do a randomized trial in a rare disease. So, you need to understand what would have happened had you not given the treatment. And I would say we are doing everything we can to make it easier for companies to succeed in the development process, while also having to make sure that we keep the same level of quality. It is quite a challenge, but I think we have learned a lot in how to do it. And as I have already mentioned, I am hoping this influx of new people will bring in a lot of really bright people who are highly motivated to think of even more exciting new things that we can do.

"Societal interest in this 40 years ago got to the point the Orphan Drug Act was passed by Congress. It puts into place a number of incentives for the industry."

Erika Berg (*host*):
That is incredible. Shifting gears a little bit to a bit more of a global perspective, how does the FDA collaborate with international regulatory agencies since rare disease is a global challenge? To what extent are standards and processes aligned sort of across different international bodies?

Robert M. Califf:
This is an interesting year to talk about international collaboration. It is rough out there in terms of what is going on around the world, and yet there are a number of really strong collaborations that we have. And I think for rare diseases, it is really important to first just keep in mind there are almost 8 billion people in the world now. The United States is only about 4% of the world's population. So, when we think about a rare disease from a US perspective, if we need more people in order to create a bigger market or get the clinical trials done, create more excitement in other parts of the world for the science that is needed, we need to have global collaboration. It starts with the EMA because of the longstanding relationship between FDA and the EMA, which regulates drugs in Europe. So, we have what we call a cluster, which is a situation in which the two organizations can exchange confidential information in the midst of drug development. Just a thing to mention there, which there is no reason people should have to think about this too much, due to patent laws and the fact that in order to recoup the investment that goes into it, companies need to be protected from having competitors develop a bunch of competing drugs all at the same time. A lot of the information during drug development is confidential, and not available to the public. To share it across countries requires that we have very tight agreements on what could happen. It is actually a crime for anyone at FDA to leak confidential information, we are really careful about that. I was just in India; 1.4 billion people just in India alone. I think everyone is aware about the tremendous creativity in the Indian population. Now, if you look at our tech companies and many of our pharma chemists who are really good at making new drugs, they either come from India or are first generation. So, I am looking for more collaboration with places like India to make this possible. The goal is to speed everything up. If it is a rare disease in the US, it is going to be a bigger population if we can include the whole world.

Erika Berg (*host*):
What would be the benefits or challenges of harmonized international standards? To put it another way, so we have medications that have been approved here, but not something we can get say overseas and vice versa. Is there any thought or push to sort of create an international standard where you could have sort of a universal approval for these, for rare disease cases?

Robert M. Califf:
I think many of us share a dream that there would be a great data repository in the cloud, which is technically trivial now. 10 years ago, if I had said that, people would have said, what are you talking about? But now we know that cloud computing is designed to keep data secure in a place where anyone with permission can get ahold of it. But then the next step is to make sure that we reach agreement on what the standards are for what should constitute approval of a drug. They are not that different around the world. In fact, the FDA is the only international agency that does independent analysis of the data so that when a company does a study it actually has to submit its raw data to the FDA, and so FDA's statisticians and scientists can make sure that it is all right. In almost every other country the data gets submitted by the company and it is accepted, but people really depend on the FDA to do that independent analysis. So, we are getting closer and closer to that dream, but we still have a ways to go. There is rivalry between companies and everything has to be agreed to. You are really talking about treaties when that happens between countries where there are a lot of other interests in play. So, it is a dream, but it is not unrealistic because technically it was unrealistic a few years ago. Not so now.

"FDA is the only international agency that does independent analysis of the data."

Erika Berg (*host*):
What risk-informed strategies does the FDA have in place to streamline the approval process for rare disease treatments

given the urgent needs of these patients? How do we de-risk the process, the approval process for rare disease treatments?

Robert M. Califf:
You are really talking about de-risking at the same time we speed it up. That is two contrary thoughts and I think a key to this gets back to the incentives. The accelerated approval pathways, and we have several of them, are intended for situations where there is a disease that has lethal or very serious health consequences for which there is not an effective treatment. The American people have spoken that they are willing to take more risk in that situation in return for earlier access to the treatment, and so in that case, we do not require the same level of clinical evidence.

> ***"The accelerated approval pathways, and we have several of them, are intended for situations where there is a disease that has lethal or very serious health consequences for which there is not an effective treatment."***

That is, if we can find a biomarker, a measurement that you can make about an enzyme or genetic product, and it seems highly reasonably likely that that will predict a better clinical outcome, then this cuts years off the clinical trials that are needed to go with that biomarker instead of doing the full-blown clinical trial. But in return, after that accelerated approval, there is a requirement that the studies actually get done to prove that what is reasonably likely is the case. There is always a trade-off here, and the de-risking in the case of rare disease is mostly related to making sure that those follow-up studies get done. While you have to prove for an accelerated approval that you have improved the biomarker, you have not proved that you actually are improving the disease's outcomes. It is a balance of these things. It is exciting and intellectually a lot of fun to work with, but the consequences, obviously, for families and people with rare disease are extraordinarily serious. It is something that we are constantly working on at the FDA.

Erika Berg (*host*):
Can you speak about the FDA artificial intelligence initiatives and how that is being thought of in terms of streamlining these processes?

Robert M. Califf:
It is a great week to ask that question since the President's executive order on artificial intelligence was just signed a day before yesterday. I had a chance to go to the ceremony. It is always fun to go to the White House and be part of something that is momentous. I had a chance to work at Alphabet and Google between my FDA stints and saw the power of computation and what it can do. So whether we are talking about drug discovery that is identifying an appropriate target, or whether we are talking about protein biology, the way proteins fold and unfold; this can now be done through computation. I heard that each dissertation would be one protein but now you do an entire array of proteins in a very short period of time with computation.

This also pertains to designing clinical trials and making sure that you do a simulation of the clinical trial before you start to make the trial as efficient and effective as possible. I am a clinical trialist by profession and a clinician. I hate it when someone does a clinical trial, does the experiment in people, which you have to do and at the end of the trial we do not really know because it was not done well enough. Artificial Intelligence (AI) pertains to this whole spectrum from discovering the drug to how the clinical trials are done. We have not talked about gene editing, which is one of the most exciting parts of this right now. We just had our first advisory committee on a human gene editing treatment. This one is for sickle cell disease. We have a deadline to make the decision about whether it goes on the market coming up shortly. We are now in the era where we can go in and snip out genes and insert genes that might be preferable in a person with a serious disease. We expect to see a bunch of these, but then we have to follow people for 20-35 years. Now we have to make sure that we understand what the consequences are of editing the genome, just as one example. So, I am very excited about AI. Of course, we have to regulate it because it could also be used for bad purposes, which is something we all need to pay attention to.

> ***"AI pertains to this whole spectrum from discovering the drug to how the clinical trials are done."***

Erika Berg (*host*):
How does the FDA work collaborate with rare disease patient advocacy groups?

Robert M. Califf:
We at FDA have been really focused on patient advocacy groups for quite a while now. We have structured sessions for patient-focused drug development, for example, where patient groups come in and talk about what it is like to live with a disease. It is actually kind of amazing. If we went back 30 years, you would find a lot of drugs being developed by scientists who are imagining what the patients needed, but not actually talking to the patients. That is kind of a mistake.

> ***"We at FDA have been really focused on patient advocacy groups for quite a while now."***

So now, whether it is a drug or a device, when a company comes to visit FDA for the first time saying, "We think we have an effective treatment for something, and we would like to start that pathway of doing the development in clinical trials," One of the first things we say is, "Have you talked with people that have the disease?"

Of course, it goes beyond just listening. We are advocates for patients being involved in the clinical trials. It is one reason that now we talk about participants in trials, not subjects of trials.

Being a human subject implies that you are just an object who is being dealt with in the clinical trial. A patient should be involved in the design and execution of the clinical trials, and then after the trial in the dissemination of the results; so pretty much throughout the spectrum. We really believe that patients need to be involved if we are going to develop the right treatments, and the right diagnostics, which is an increasingly important part of this; so-called Diagnostic Odyssey that we hear more and more about. Getting the right diagnosis is absolutely essential for getting the right treatment, but sometimes that takes years to decades and it is something we have to fix.

> ***"We really believe that patients need to be involved if we are going to develop the right treatments, and the right diagnostics, which is an increasingly important part of this."***

Erika Berg (*host*):
I want to explore a little more about the FDA being an advocate for people in their clinical trials. What is the FDA's role in advocacy overall? In what other ways is the FDA involved in advocacy work?

Robert M. Califf:
Well, first of all, I would like to say that it is a complicated thing because our primary role in society is to be the judge of what gets on the market, particularly when it comes to drugs and devices, because there is a history of people selling things that did not work and were dangerous. You think about thalidomide, which was one of the sentinel cases of actually giving away free samples of a drug that caused fetal malformations or children with birth defects. When you are a judge, you have to be impartial. While we advocate for good treatment, we do not advocate for particular treatments because we have to do a scientific assessment of what the evidence really shows. When you think about referees in a sport, the referees are some of the best advocates for the sport. They study it, they love it! We cheer when a company develops a new treatment, and we encourage patient groups to be involved and participate. The more participation there is, the faster the trials get done, and the more likely it is that if there is an effective treatment and we can get it on the market. We are advocates in general, and we are advocates to anyone who comes to us to be involved in the process. But we cannot advocate for a particular treatment until we have made that assessment.

Erika Berg (*host*):
We talked a little bit about gene therapies and some of these very advanced and emerging technologies. But what initiatives are in place to encourage the development of these novel sort of cutting-edge therapies, precision medicines for rare diseases?

Robert M. Califf:
We have a number of programs within both the Center for Drugs and the Center for Biologics that I would say supplement the primary role of NIH in the industry, which is to develop these platforms and technologies. Scientists sometimes get off in their own world; there is a real value in discovery science, just for discovery's sake. That is, you have no particular interest in mind other than you love the science and you do it. But if you want to develop a treatment for a disease, you have got to focus in on the places where it is going to be effective. The FDA has a real role there in interacting with the NIH and the academic community. We are also very excited about platforms about messenger RNA vaccines. That was 20 years of work by the scientific community, both in industry and academia but with the FDA playing a key role in moving it to the point where when the pandemic hit, we were ready to go. A lot of things that would have taken a very long time were done quickly because we were ready. Gene editing is going to be a really good example of that. It is happening already because if you think about gene editing, it is like you have a razor blade with the same razor, but you are putting in a different blade to edit a particular gene. Think about 7,000 diseases; we do not need 7,000 platforms. We need a lot fewer platforms that will cut a lot of time off the review cycle, because we do not have to evaluate each platform every time, but the particular application of that gene that needs to be evaluated.

> ***"We are also very excited about platforms about messenger RNA vaccines. That was 20 years of work by the scientific community, both in industry and academia but with the FDA playing a key role in moving it to the point where when the pandemic hit, we were ready to go. A lot of things that would have taken a very long time were done quickly because we were ready."***

Erika Berg (*host*):
What steps is the FDA taking to ensure that orphan drug designation and incentives are used appropriately and not abused by pharmaceutical companies?

Robert M. Califf:
I could give a long talk about this, but I will keep it short. It is a constant tension in the United States between making a profit and serving the health needs of people. You see it every day right now in discussions that go on about the cost of pharmaceuticals as an example. But in the case of orphan drugs, we have a law that says you are protected, as an incentive, for the use of that drug for a particular indication and just as one example, we have found that some companies have tried to use that to block other companies from developing the same drug for a different indication, but they are not actually developing that different indication. If you are a patient who needs that drug, that is not fair. We look for all the loopholes that companies use, and I have been on the boards of biotech companies in my previous work, and so I have

heard all the arguments. It is understandable that people want to make a profit, but part of our job at FDA is we are a public health agency; so, our primary interest is the patients, not the financial profits of the companies.

Erika Berg (*host*):

I saw a statistic the other day, and it spoke to me. I have read that about half of people diagnosed with a rare disease are children and so what words of encouragement do you have for those parents?

Robert M. Califf:

Well, first, I would say there is always hope. I know the feeling because when I was an intern at University of California, San Francisco, our first child – our daughter at the age four months – I was told in the course of 24 hours that she had congenital heart disease and had a very low chance of surviving. In her case, it worked out well. She is an adult and now has a daughter who is a sophomore in college against the odds. That was just when cardiopulmonary bypass as a technology was coming in and I happened to be at a place which was leading the field. If that were not the case, it would not have been that way. We are all at the FDA very aware of the press for time and the need to be as quick as we possibly can, because when a lifesaving therapy comes in, you want to make it available. The fact is that science is moving very quickly now and there are going to be more and more of those opportunities. We have to be ready to take them when they come and participate, so there is always hope. We are listening at the FDA. Do not worry about us. We can take it. If you have things that you think we can do better, let us know. We are trying to do our best, but we also know we are not perfect. So, hang in there and let's all hope for the best.

> ***"There is always hope […]. We are all at the FDA very aware of the press for time and the need to be as quick as we possibly can, because when a lifesaving therapy comes in, you want to make it available."***

Erika Berg (host):

Thank you so much. If you would like to send your thoughts on this webinar, please email webinar@aaas.org

Thank you once again to our guest and to Fondation Ipsen for enabling this conversation through their kind sponsorship.

Advocacy in rare disease: Surveying the landscape

The plight of patients with rare diseases is critically undervalued in healthcare. The statistics are frightening: There are 7000 rare diseases in the world that collectively affect 350,000,000 people. One in 11 Americans has a rare disease. Three-quarters of patients with rare diseases are children. Only half of patients receive an accurate diagnosis. The average delay for a patient to receive a diagnosis of a rare disease is 1.5 years. One in four patients with a rare disease waits 4 years for an accurate diagnosis.

There is an urgent need to advocate for the millions of people worldwide living with rare disease. Advocacy, defined as the public advancement of a cause, has many facets, and includes campaigning for more research funds, activism to eliminate discrimination, lobbying governments to improve access to healthcare, and crusading for the needs of patients' caregivers.

In this first webinar in the 2023 Science/AAAS Fondation Ipsen series on advocacy in rare disease, we examine the advocacy landscape, asking: what does advocacy entail, who are advocates, what organizations are involved with rare disease advocacy, what determines how umbrella organizations allocate resources, and what is effective—examining success stories of when advocacy has worked.

Panelists

Flaminia Macchia, M.A.
Roche, Brussels, Belgium

Michael Manganiello
Pyxis Partners, Washington, DC

Marc C. Patterson, M.D.
Mayo Clinic, Rochester, MN

Durhane Wong-Rieger, Ph.D.
Canadian Organization for Rare Disorders (CORD), Ontario, Canada

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

The Conversation

Erika Berg (*host*):
Hello everyone and welcome to this first webinar in our 2023 Science series on advocacy in rare disease entitled Surveying the Landscape. I am Erika Berg, director, and Senior editor for Custom Publishing at Science. I will be the moderator for this discussion. This is our third year exploring the challenges and successes in the rare disease field. In this first webinar, we will shift our focus to advocacy and take a broad look at what advocacy looks like in the rare disease space. Who are the players? What can organizations bring to the table? What can we learn from successful advocacy campaigns from outside the rare disease space?

Durhane Wong-Rieger:
My name is Durhane Wong-Rieger, I am president and CEO of the Canadian Organization for Rare Disorders. I am also chair of Rare Diseases International, our global Alliance of Rare Disease Organizations. I am actually in Geneva, Switzerland, just coming back from an open session with the WHO on the Essential Medicines list and was advocating there for the inclusion of rare disease drugs within WHO essential medicines.

Flaminia Macchia:
I started at Roche on 1st of March as Senior Global Patient Partnership Director, dedicated to Huntington's Disease. I am also the former executive director of Rare Diseases International, so Durhane is my former chair. I have been an advocate for rare diseases for the past more than 20 years. The views that I will share during this webinar are my personal views.

Michael Manganiello:
I am Michael Manganiello. I am the CEO of Pyxis Partners. We are a professional services firm that focuses on public policy engagement advocacy. I think one of our primary goals is diversity in clinical research, which is quite a big problem. I am honored to be here with such impressive panelists, scientists, and doctors. I, however, am not any of those. I guess my strength is my role as a patient advocate and that is what I have spent my whole career doing, in three different avenues. First, I have been HIV positive for 35 years, so HIV was the beginning. Second, I ran the Christopher & Dana Reeve Foundation for a decade, learning about the challenges of spinal cord injury and research, care and cure. Third, I work for a lot of organizations, all from the spectrum of patient advocacy. I am honored to be here today. I am probably going to talk about different kinds of models of advocacy than rare diseases, although I have dealt with the rare disease populations many times over the years, including NORD.

Broadcast Date: 4 May 2023 **Access this webinar here**

Marc C. Patterson:
I have had the privilege of working with children and families with rare diseases for the last 30 years since I was a fellow at NIH. I am currently a professor of neurology, pediatrics, and medical genetics at Mayo Clinic. The focus of my work is on inherited metabolic diseases in children, particularly lysosomal disorders, and congenital disorders of glycosylation. I have to say one of the highlights of my career has been the opportunity to work with advocacy organizations: not just because you feel you are accomplishing something that is useful, but because of the tremendous energy and enthusiasm of these groups and the huge need there is in this community.

Erika Berg (*host*):
Advocacy is defined as "the public advancement of a cause". That is basic definition. Michael, how do you define advocacy?

Michael Manganiello:
While advocacy is a great word, I think of advocates as more powerful than that. I think of them as activists, because to be successful at promoting whatever cause you are trying to advance, you have to be passionate. You have to get people's attention. You have to hold people accountable. You need to find leadership in people that will stand up for your cause. You must mobilize your community. Advocacy is a great word, but it is not big enough for me.

> ***"I think of advocates as more powerful than that. I think of them as activists, because to be successful at promoting whatever cause you are trying to advance, you have to be passionate."***

Erika Berg (*host*):
Great. Does anyone else have a different idea about advocacy?

Durhane Wong-Rieger:
I am a psychologist by training, I taught for about 20 years. I have two children, both with rare disorders. So, we started off advocacy. My daughter had an undiagnosed disease. As a personal advocate, you are forever trying to get a diagnosis, trying to get attention, trying to get support from a system which (even if Canada has wonderful healthcare system) has no capacity for dealing with people that fall outside the norm. So, I agree with Michael, you are an advocate.

I have also spent many years as an advocate for hemophilia and HIV - that was my early start. And we were definitely advocates! We were on the picket lines. We were helping to launch lawsuits. We were fighting for access to therapies. I also learned how to be an inside advocate as well as an outside advocate. It is one thing to be making a noise outside, and another to really being able to get attention. You can make as much noise as you want outside, but unless you can get into the room and at the table, you are not going make a significant change. So, we have learned a whole lot over the years that there are many shades of being an advocate. There are many ways of being an advocate, and there are many different people that must come together to make advocacy work. The biggest challenge is not so much getting other people to pay attention, but for us to be able to work together and not kill each other along the way.

Erika Berg (*host*):
How do we paint the landscape of players in advocacy? Flaminia, where are all the advocates in the rare disease space?

Flaminia Macchia:
Advocates are persons that support a cause on behalf of a group of people beyond their own individual interest, to promote some strategy or policy or legislative change, etcetera. The most legitimate advocates are persons living with the disease themselves, either as patients or as caregivers, family members, loved ones, and persons that are professionally involved with NGOs or civil society organization. However, from an industry perspective, there are employees who have the important role of gathering the perspectives from different patient communities in specific disease areas and bringing them within the company. The so-called "outside in". These are typically people like me, in patient partnership or patient engagement. They are advocates in the sense that they interact with patient communities outside, and then advocate internally to make this patient's input and contribution heard and acted upon within the company. These persons also have the role to inform patient communities about companies' strategy and decisions. Sometimes, they are difficult ones. This is more "inside out". These roles are highly scrutinized and must obey by a strict set of rules to ensure respect, independency transparency, and absence of in due influence.

Erika Berg (*host*):
Marc, could you give us the perspective of the medical professional in the advocacy world? What role does advocacy play in treatment and in research in the medical space?

Marc C. Patterson:
I think my colleagues have given a beautiful definition. What you take out of this is that advocacy is a team sport, that you really must work cooperatively, as Durhane said, without killing each other. I know that was said jokingly, but it is important to remember that with the sort of disorders we are talking about, passions run high. It is important to take that into account. To come back to where the medical profession fits in, we have an "inside-outside" approach as well, because within medicine, it is very important to advocate, to be an advocate for the importance of rare diseases. We are taught in medical school that things are important if they are treatable and if they are common. Well, a lot of rare diseases currently don't have treatments, although I am confident that they will.

However, getting people to understand that anyone who is sitting in your office at any time may have a rare or ultra-rare disease is extremely important. Don't discount the possibility because something is rare. I have seen many patients, and I am sure my colleagues have had indirectly the experience of being told it couldn't be this disease because it is too rare. I think of advocacy

in terms of education within the profession, as well as the community as a whole, which is a very big part of advocacy.

Iwill share one small anecdote about opportunities for advocacy, because I think you should always take them. I was at a gathering where I was being presented with an award and I had an opportunity to speak to a US senator. I thought, what can I tell this man? This gathering was about an ultra-rare disease. So, I said to him: "Senator, this is an ultra-rare disease, which probably affects 500 people in this country, but there are thousands of rare diseases, and there may be 30 million people in the United States with a rare disease." When he gave his address to the gathering, shortly afterwards, he led off with saying, "Ladies and gentlemen, there are 30 million people in the United States with rare diseases." So, I thought that it is a victory for advocacy because it gets the attention of our legislators to understand that these disorders are collectively extremely important. They constitute not just a great burden to the individuals and families affected by them, but to the community as a whole. I think that education is a key part of advocacy, and I think persistence and taking the opportunity to always be an advocate when it arises, is an important part of that role.

Durhane Wong-Rieger:
I think what Marc says illustrates a couple of things that are so important. One is obviously having people that have the ear inside, as Flaminia said, to carry that message. But also, Marc had a lot of credibility in carrying a message. It could have been a patient and it may have made an impact, but it might not have made the same impact. I think, as we are going along, life is getting as many allies as possible to help carry that message, but also knowing who the best emissary is to actually deliver that message is key. Sometimes, it is important to be able to step aside and say, "Okay, you are going to be better at this than I am." Even though I might feel very passionate about it, sometimes it isn't just the passion. It is having the credibility and not feeling threatened when somebody else actually comes forward. Again, as Marc and others have said, it is a team sport, but it takes many kinds of players as well. If we all want to pitch, then it is not going to work. We all need to be able to look at: "where is my best position, what can I do and when do I pass that ball?"

"Knowing who the best emissary is to actually deliver that message is key."

Erika Berg (*host*):
Durhane, could you share a little bit about what the role of an umbrella organization like CORD is in the advocacy landscape? How does your organization work? How do you deal with advocacy issues when you are representing so many patient advocacy groups?

Durhane Wong-Rieger:
You are asking me at such an exciting time in Canada. The Canadian Organization for Rare Disorders is a little cousin to NORD, which is the big umbrella organization in the US. We have tucked ourselves behind NORD. We have also tucked ourselves behind Europe's EURORDIS. In Canada, we have been fighting for many years trying to get rare disease strategy and to get recognition for rare diseases. As I said, we have great universal health coverage. That means, though, that in some cases, there is not a real interest in looking at very small and rare ones, because we are looking at the "big popular" ones. We have been fighting for many years trying to get a rare disease strategy, following the models of others. About a month ago, we finally got the announcement that government has grieved that they are announcing what they promised about three years ago: $1.5 billion to invest in a rare disease drug strategy

It is not insignificant. I say to my American friends that it is Canadian dollars, it is only about three quarters of a US dollar, but it is okay! It still means a lot to us. To get there, we had to bring in all the players. That means getting the researchers, the clinicians, the pharma companies, and policy makers all lined up. It was really the case that CORD led the way and also led the fight for what that strategy ought to look like: that it really needed to serve the needs of the people comprehensively and to be able to get everybody to hold the line to agree on what those core concepts or principles would be, and to agree to work together in that environment. Those are things we learn from other organizations. We are about one hundred organizations in Canada. Our task was to keep everybody moving together, in part because some diseases had access to therapies early on, some diseases had access to much better diagnosis and treatment. But not all the diseases; most of the diseases don't have anything. So, how do you get people to say, "We want to be part of this and we recognize this is happening, but we don't have a diagnosis, we don't have treatments yet. We all need to be part of it."

This is something we learned a long time ago, when we were first doing hemophilia, or HIV. The challenge was that there were some people that had the good version of HIV and some people had the bad version of HIV. We had to stick together and say, "HIV is HIV and everybody is in this together". I think that keeping everybody together, even though we are all in different places and people have different needs, was a crucial role we had to play.

Another important thing is recognizing that it is not a zero-sum game. The minute we get into the trap of what governments and health systems like to do, such as "we don't have so much money; we can fund this, but we can't fund that; we are going to go to here and we will look for those results."… That is not the answer. As a community, we must stick together. You must remember who the enemy is. The enemy is not each other. The enemy is out there. As long as we stick together, we can win. At the minute we start to allow ourselves to be pulled apart, we are going to get nothing. That is going to let everybody walk away and say, "See, we told you so."

"I think that keeping everybody together, even though we are all in different places and people have different needs, was a crucial role we had to play. Another important thing is recognizing that it is not a zero-sum game."

So, the biggest part with working as an umbrella organization is getting everybody to stick together and to follow a common message. That means that we must also listen really hard. We can't just say, "Okay, come in this direction. I know what is the right thing to do. You follow me." How do we listen to 150 different countries at 85 different organizations on the global level, with some people on low and middle income and some people on high income? How do we make sure that we are having that same global message? We do it part by listening to everybody and making sure that we are paying attention. I can get anybody do anything I want so long as I am listening to what they need.

"The biggest part with working as an umbrella organization is getting everybody to stick together and to follow a common message. That means that we must also listen really hard."

Michael Manganiello:
Durhane, what you said is so critically important. Particularly in the beginning of the days of HIV: we were so desperate, but we had leadership. Suddenly, we started to get funding. Then, we were getting too much funding and the other disease groups were asking, "why is HIV getting so much funding and we are not?" We called the Summit, bringing together all the groups, and we said, "look, the higher the water, the higher the boats float." It was a little bit more complicated than that, but people finally got it. They understood that because of HIV advocacy, we were the ones that led the way for accelerated approval for parallel tracks so that diseases of any kind have that same access. Even to this day, when COVID hit, the mRNA vaccines are a product of the work that was done during the days of HIV. So, you just never know what is going to lead to what. So, you all must be on the same page, rowing the same boat in the same direction. I couldn't agree more.

Erika Berg (*host*):
Flaminia, are there differences in approaches or even definitions of advocacy depending on where in the world you are?

Flaminia Macchia:
Yes. Rare diseases organizations may be very different. They may have different sizes, different resources, different maturity levels or political sophistication to feel empowered to talk effectively with policy makers. But at the end of the day, I believe that the objective is always to try and make rare diseases as a policy priority. Most challenges are shared everywhere and across rare diseases. In the end, we are all talking about the lack of knowledge and information, the lack of experts and expertise, the lack of investment, challenges in accessing diagnoses, social medical care, diagnostics, high quality medicines, etcetera. However, from my experience at RDI, I have seen some regional specificities. Very broadly speaking, the European approach tends to be more holistic and integrate more the medical and social care aspects with patient representatives progressively being more involved in the value assessment of new health technologies. The African approach focuses more on awareness raising of rare diseases as an issue and health system financing and strengthening, starting from primary care community workers, continuity, and integration of care. Africa is awakening to rare diseases thanks to the dedication and dynamism of some young HCPs and some emerging Civil Society Organizations. Now, we also have the newly established African Medicines Agency, so that may be a step in the right direction. I am going to dare saying something about Asia, even though Durhane is here and she will be able to say much more about it. Asia is very complex. It covers countries that are extremely different in size, income levels, healthcare systems. In Japan and Bangladesh, I think the focus remains on access. In Latin America, I believe that access to therapies and diagnosis remains the key focus. There is this a very specific Latin-American trend, which is a judicialization of care with people who can afford it, going more and more to court to get access to treatments. This reinforces inequalities. I will let Durhane step in.

"I have seen some regional specificities. Very broadly speaking, the European approach tends to be more holistic and integrate more the medical and social care aspects with patient representatives progressively being more involved in the value assessment of new health technologies. The African approach focuses more on awareness raising of rare diseases as an issue and health system financing and strengthening, starting from primary care community workers, continuity, and integration of care.

Durhane Wong-Rieger:
You have done it brilliantly, Flaminia. You have also alluded to an important topic, which is the political context. I am interested in Michael and in Marc's perspectives is this. We know that across Asia, even though it varies in terms of income and access, there is a strong sense among many patients that they don't have a right to healthcare. In America, there is a strong sense that we have a right to advocate. Whereas in many cases, in Asia, you have to get people there to feel like they can and need to speak out. It is not only their right to do so, it is important to do so. So, I think that there are a lot of deference there, even at the individual level. That is what my healthcare professional says. That's what the government says.

I believe Latin America is kind of the opposite. There is a strong sense that we have a right to, but there is a political squashing of it depending on the political environment. As you say, it is a very litigious environment where people have a right, but the answer is: "You have a right to it, but you must sue me for it. If you can sue me, you can get access." Anybody can get access as long as they can sue, which is a strange way of doing it. I would love to hear from both Michael and Marc, because the texture in the US is so rich. You can go from one sector to another, depending on how you look at it. The different layers that exist in terms of people, ethnicities, income levels and educational levels… I would say that is about as rich as you would get globally in terms of advocacy and people and how they actually approach and get access to the system.

Marc C. Patterson:
You have expressed it so well Durhane, and it is true. I wish I could say that everybody in the United States had equal access to care, but we know that is not the case. So, we have a lot of cleaning up to do in our own backyard. Equally, there are other countries where I think people are good advocates. It happened that I was in Vietnam last week and visiting the Women and Children's Hospital in Da Nang. I saw a child with Pompe disease receiving enzyme replacement therapy. I must give credit to the pharmaceutical industry because the family who were great advocates for this child were able to access this very expensive therapy through an outreach program - would be the manufacturer. I think the point is inclusiveness. We have to work towards access. In rare diseases and ultra-rare diseases, one of the ways that we achieve inclusiveness is to make sure that as many countries as possible have the opportunity to participate in research. This is because if we are going to research ultra-rare diseases, we must work together internationally to have a chance of capturing a patient population, so that we can execute studies. So, I think that is a great opportunity for our advocacy to advocate for opportunities to participate in research. That is one way we can work together.

The political aspect is very important. In the United States we now have a Rare Disease Caucus. There are members of the Congress who get it, who understand, who are receptive. I think we must work with them again in a cooperative fashion, ideally as a united rare disease front to the greatest extent we can, but also taking advantage of the stories of individuals and families, because they are powerful. We must never discount those as part of the whole framework.

One other aspect of research I mentioned, which combines advocacy, is the way that rare disease communities for specific diseases can come together internationally. I will give you the example of the International Niemann-Pick Disease Alliance: an ultra-rare family of diseases for which a number of national groups have come together under this umbrella, which permits sharing of information on research. In addition, they have set up a registry. This is not unique, but it is a new model, because it is a registry which is owned and controlled by the advocacy group with participation of academics and industry, so that it will be an ongoing sustainable resource for that community. I think this is terribly important because we know that in academic medicine, sometimes registry data is lost, for example, if someone loses a grant or retires or moves out of an area. In industry, once a registry has done its job, for example, for approval of an agent, it may also then be lost. This data is precious, and I think we must do everything we can to preserve it. That is one model where advocacy has been key to developing a sustainable resource for a rare disease community.

Michael Manganiello:
I think the West has an oversized influence over African countries and the poor nations. I think one of the challenges is - and I know Flaminia is going change everything at Roche - that Pharma has not been the greatest player in all of this. Up until now clinical trials had been done on white straight men. President Obama's signature scientific initiative was the All of Us Research Program. We luckily got the engagement award. We built a network of trusted partners across this nation from Black churches to YMCAs - people that minority populations that are underserved in biomedical research populations listen to and trust. There is a lot of mistrust of science. We have now genetic data on almost 250,000 Americans, the majority being minority populations.

An interesting story, where the politics are important, going back to the HIV/AIDS days, is when Dr. Fauci stood up and members of Congress stood up and made the difference, because that is where the funding comes from and that is where the leadership is going to come from. That is also where PEPFAR came from, which was the international initiative to help people with HIV in Africa. Until Dr. Fauci went over, scientists then said, "What is the point of getting antivirals to Africa? They can't tell time. They don't wear watches." Dr. Fauci got there, and we have changed the face of Africa regarding HIV/AIDS. That took leadership politically, scientifically, people like you. I believe we bring our own prejudices with us to these other countries, and we must stop that. We must think scientifically, and the voice of the patient is critical in all this. I have to say I haven't been on a panel this exciting in a long time, so thank you all.

Durhane Wong-Rieger:
Marc, I think you are in serendipity. I just got a note in my inbox connecting me with the name of PICKS community here in Canada. We are looking to do some advocacy for submission for a new therapy. I wrote back and said we need to reach out to the US, because we don't have a big enough community here to actually have the information of people that have been on this therapy. So, I am going to catch you! This is what we need to do. This is, as Michael is saying, how the disease community works. We reach across, we help each other. There are no barriers between patients and patient organizations. I know they are going to respond and they are going to give me all the help that they can. That is great, because now I don't have to go searching for where can find his name in the PICKS community. Erika, if nothing else, this has been a great opportunity for me to help get a need met right here right now.

Michael Manganiello:
I think this partnering and cooperation among diseases is critical. When we were in the middle of the embryonic stem cell debate, petrified that the federal government was going to shut the door to federal funding, we were so successful. We kept the door open. We passed the Stem Cell Research Enhancement Act. Unfortunately, President Bush vetoed it twice, but that is okay. We kept the door open enough, but we brought patient advocates in from all over the country. These people were smart and were underestimated, because they were so knowledgeable of their own disease. We brought in a woman called Elizabeth whose daughter had Rett syndrome, a terrible disease that strikes little girls. By being part of this larger broader coalition that supported stem cell research, Elizabeth and her daughter in a wheelchair testified before Congress. This raised awareness to Rett syndrome by levels that had never been raised before. I do think this cooperation is so critically important.

Durhane Wong-Rieger:
And the first therapy for Rett is now out.

Michael Manganiello:
I will let the STEM Cell Coalition take a break.

Durhane Wong-Rieger:
We haven't got access to it yet but it is there and it has been approved.

Michael Manganiello:
That is fantastic. I didn't know that. I am thrilled to be hearing that.

Durhane Wong-Rieger:
It is a long road. Hopefully Elizabeth and her daughter can figure out how they can get access, or maybe they can do clinical trials. This is amazing!

Marc C. Patterson:
I would like to make one more comment about this in terms of research, just to reinforce what you have said. It is so important to listen to the community, because for so long, one of the big problems in medical research was the fact that our outcomes would be things we could measure because they were easy to measure. But they were not necessarily what really mattered to the patients. One of the most exciting parts of my journey has been learning from my patients. They are my greatest teachers. I have had great professional teachers, but they don't match the patients and the families. I think we must listen to them. Fortunately, there is some awareness of this. The patient-focused drug development groups at the FDA are a great development. They must listen to them. It is a start. I think taking patient-driven outcomes into account makes a huge difference because they are not always easy to measure. For someone with a devastating neurological disease, the ability to make transfers may be a huge difference in their daily life. Even though it is not easy to measure, it is not a traditional outcome. I think this is just another aspect of advocacy where we are working together, and it is a reciprocal relationship that is going to drive the field forward.

"It is so important to listen to the community, because for so long, one of the big problems in medical research was the fact that our outcomes would be things we could measure because they were easy to measure. But they were not necessarily what really mattered to the patients."

Michael Manganiello:
Just one final tip to Marc's great point. During the HIV/AIDS crisis we smoked or bombed the campus of the NIH and left flyers everywhere. Dr. Fauci picked one up that had a lot to do with the science and aspects of clinical trial design. He read and he goes, "This is kind of interesting." He told his scientists his team, "We are going to bring some of these activists in." They replied, "You are not bringing these activists in. We are not meeting with them." Then Dr. Fauci said, "Well, you either meet with them or you don't have a job." Ultimately, what happened though was that patients became part, or at least had input into clinical trial design. It was critical. Not every HIV patient was that smart or got that smart, but a small group did get that smart and smart enough and it made a big difference. To Marc's point, patients know what they know.

Durhane Wong-Rieger:
Can I say the negative side of listening to patient reported outcomes though, Marc? Sometimes it makes an impact and sometimes it doesn't. Right? That is the real challenge. We had a young man who was 26 years old with SMA. He had come much later than the early treatment. So, he is already in the wheelchair. There is a new therapy that is out. It is funded and approved for patients up to 25 years old. He is 26. Guess what? They are saying no to him. He actually made a documentary. He has been able to come in and do the testimony. He has enough movement in just one hand to continue to operate. He has an extended arm. He was able to demonstrate what he could do with this extended arm. Guess what? They still said no.

It breaks your heart when you see this. Then we put the poor company in a bad spot because they are basically saying to the company, "Why don't you just give him the drug?" But at what point do you stop? "If I give him the drugs, then who else do I give the drug to?" He is an amazing young man. They are saying it wouldn't make a big difference. "We don't see you getting mobility back. You are not going to get out of that chair and walk again." All I want to do is have enough movement in one finger. So, I operate my robotic arm, using my computer and he can do it. He can demonstrate that. This arm is so amazing. You can put mascara on with it (not that you put mascara on). And yet we are still saying no. I hope that somebody from our province of British Columbia is listening to this and feels ashamed.

Marc C. Patterson:
Well, I think that really speaks to the whole issue about flexibility and where do you draw the line. I understand the point because we find ourselves on either side of this. I don't think there is an easy answer. I think we have to rethink the way we make rules about these things, and we have to be more individualized. One of the things that the Rare Disease Community is bringing to biomedical science overall is the appreciation that one size does not fit all. Every week, we are identifying new diseases. I think we are recognizing that many common syndromes are really families of rare diseases, which is why our therapies don't work very well. So, when we truly have precision medicine, we are going to have to have individualized outcomes.

I think the point you have raised is extremely important. How do we have a way of ensuring that we can measure an outcome in an individual to achieve a meaningful improvement? Of course, there are issues of cost and I understand that they are always behind this. However, I think you raise a really important point that maybe the whole community needs to think differently about this. If rare diseases teach anything, it is that one size does not fit all. We really must tailor the treatment and the measurement of the outcome to the individual.

"If rare diseases teach anything, it is that one size does not fit all. We really must tailor the treatment and the measurement of the outcome to the individual."

Michael Manganiello:
Durhane, talking from the exact point of view of the patient: give

them the drug. That is why there are parallel tracks. That is why there is compassionate use. The FDA doesn't look at that data on the compassionate use side. They only look at the trials. You have nothing to lose. That kid might keep his finger. Give him the drug. Sorry, I got all activist.

Erika Berg (*host*):

That is the energy we want here. Michael, would you have examples of successful strategies that you have used to advocate for people living with HIV/AIDS?

Michael Manganiello:

I just went on Cabenuva for 30 years. I have been on thousands of pills a day for 32 years, and now I get one shot every two months. Many years passed, but a couple of years ago, I started hearing other patient advocacy groups. Act Up was our big advocacy group – the one that was doing the smoke bombing and all that stuff and that was getting the attention. Was it just a moment in time, with the million young men dying, or were there any lessons to be learned? I wrote a report on it called Back to Basics. I interviewed everyone, from Jim Kern from the CDC to Dr. Kessler, who was at the FDA, to Peggy Hamburg, who was Tony's assistant, to a lot of other people, to Dr. Fauci, to Larry Kramer. There were key lessons. One of them was getting attention. To your point, it is not just about getting the attention. What do you do when you have the attention? You have to bring knowledge and solutions to the table. You must mobilize your community, which is what we did. You must hold people accountable. That is also what we did. It was sort of growing leaders: political, well-known people, actors, anyone that can get attention and can keep the momentum going. Those five steps are still applicable today and can be followed today. I will send the three of you, the report I wrote - I think you will appreciate it and enjoy the read. We had such great success. Today, people are still getting HIV today, but it is a manageable chronic illness. It is not a death sentence, and that is a success. We did lose half a million young men, that is not great, but we are here, I am here. So, I consider that a big success.

Erika Berg (*host*):

Flaminia, I know you haven't been at Roche for that long, but you have a long history in advocacy in rare disease. Is there a success story you have had at Roche or from your previous work that you would like to share?

Flaminia Macchia:

First, you mentioned, "One size does not fit all.". I would also add that one player cannot change it all alone. So, thinking about the role that industry can have in advocating for rare diseases, industry has the primary role and responsibility to deliver high quality medicines to patients. From there, there is obviously the role of continuing to invest in rare diseases and continuing to develop these medicines, healing more and more patients, and advancing science for all. That means that industry needs to keep on talking and taking insights from people living with rare diseases themselves. I would like to underline that industry also has a say with other players in the overall debate about healthcare system restructuring and strengthening. I think we need to tackle all of these issues about access and advocacy for rare diseases within the broader frame of social justice and identify together where changes and savings can be made, and look at healthcare systems as a whole and as an investment in healthier society rather than only as mere costs.

"One size does not fit all.". I would also add that one player cannot change it all alone. So, thinking about the role that industry can have in advocating for rare diseases, industry has the primary role and responsibility to deliver high quality medicines to patients. From there, there is obviously the role of continuing to invest in rare diseases and continuing to develop these medicines, healing more and more patients, and advancing science for all. That means that industry needs to keep on talking and taking insights from people living with rare diseases themselves."

Second, when it comes to an experience in terms of successful advocacy, for rare diseases, at the international and global level, the adoption of the UN resolution was a big success. It demonstrated that, with all the differences that we mentioned, including regional and country approaches, we can work together at global level and be impactful. We can share a couple of ingredients for a successful recipe. I believe it starts with clarity of the overall purpose and shared objectives within realistic timelines. The agility to adapt to unforeseeable circumstances such as COVID was also crucial. We were able to get to the UN resolution on rare diseases during COVID times. Nobody really expected us to succeed. It is also important that one organization takes the lead and coordinates the campaign and to have consistent interactions between the local level, national level, regional level, and global level, while building capacities and mobilizing the grassroots and reaching out to policy makers in a coordinated way. I heard someone else saying it that, "Each actor should play its own most effective role without overlapping and undermining each other and never give up."

"Each actor should play its own most effective role without overlapping and undermining each other and never give up."

Erika Berg (*host*):

Marc, do you have a story to share? One example could be the research fund set up by twins with late onset Tay-Sachs disease.

Marc C. Patterson:
I think any success I talk about is the success of others. It is the success of the patients in the advocacy community. If I have been able to play a role in that, that is very fulfilling for me. In this case, there was a family who, through their connections to the New York Times, were able to gain access to the media and tell the story in a very effective way. The funding that was gathered has been used to bring together a group of researchers who might not otherwise have known one another. There are now some very promising therapies under trial. I think that is a great example of the way that we work together in the advocacy community. That one person's success is everybody's success. Each step we take is a step forward for the whole community.

I can't match Michael's or Durhane's stories, which are amazing and inspiring to all of us. I think we can all share that as long as we all play our role and we step up at every opportunity, that is tremendously important. Another success, or what I would hope to see as a success, is just being as an advocate within the medical community to always raise awareness of rare diseases. You can do that in different ways. One of my hats has been as an examiner for the American Board of Psychiatry and Neurology. I am always pushing to have rare diseases included in examinations. And they are, and people learn about them because they know they are going be asked. That is a small thing. Raising awareness in that way is important, but it is not enough. As Michael and others have pointed out, you must have a plan. Once you have got people's attention, you must know what to do with it, and have a plan to move forward. How are we going to develop a therapy and help these people? It is not always the blockbusting drug. Sometimes, it is just access to services or recognizing that people with chronic rare diseases need habilitation services throughout their life, that it shouldn't be based on a stroke model, for example. Many examples could be given, but I think the theme is that you must be persistent and aware and work together as part of the team.

"Another success… is just being as an advocate within the medical community to always raise awareness of rare diseases."

Erika Berg (*host*):
Is there anything our audience can learn from a strategy that was not successful, an obstacle that was insurmountable or something that you have learned along the way from a strategy that may not have worked that well?

Durhane Wong-Rieger:
I don't know about a strategy that doesn't work, because you only know it doesn't work when you have played it to the end. We have just got a rare diseases drug strategy. I got the chance to stand up after the Minister made the announcement and I looked at the minister and I said, "Thank you very much, Minister. You know I gave you this proposal 10 years ago." I wasn't saying it nastily, I was just reminding him. I said, "I wrote it 15 years ago." – because I did! Sometimes you just repeatedly hit the wall. Michael and everybody else said, "You don't give up." You don't know that anything has failed. Nothing has failed until it's... I don't think it's ever over. I think we learn from each step along the way.

I think it feels like a failure, because you don't get what you want. One of my researchers sent me a little fridge mat that says, "Shoot for the moon. Even if you fail, you'll land among the stars." - it is one of the things that I remember. Okay, so I didn't get the moon, but we are up there. I don't know Erika; it doesn't answer your question because I think we all had failures. I have had tremendous failures. I have had more failures than successes, that is for sure. I have had more people die on me than I would care to count on. But those aren't failures.

We were just at the WHO meeting on access on medicines for rare diseases. One of the advocates spoke about SMA and he says, "You know what? By the time we get done with this meeting, 120 kids will have died." In Canada, a child dies of a rare disease every 39 minutes. Those are startling failure rates when you think about it. Yes, they are failures, but they are also a road towards what the success is going to be. I think that is what we must learn from this. We all have failures. We have things that we try over, and over, and over again. Somewhere along the line, as Michael says, if you are still alive, there are many, many thousands who have died.

Michael Manganiello:
Durhane, I couldn't agree more. I bet all everyone on this panel would say the same thing. Nothing is insurmountable. Yes, you will face failures, but you run around that failure. You learn from that failure. I think Cystic Fibrosis is a perfect example. It is a rare disease pharma wasn't doing research on. So, Cystic Fibrosis said, "We will do the early research. We will fund the early days research." And they did: they partnered with Vertex Pharmaceuticals. I will never forget this story as long as I live. I was at an NIH meeting and a mother stood up told the story. They had their early first successes, and I think it was successful - maybe 7% or a very small percent. It is bigger now. The mother stood up and said that her son - of course, they just assumed he needed to be percussed - told them he didn't need to be percussed. That was an organization that hit a wall and figured out some other way to go around that wall. Now I think it is up to 14%. I think with God's willing. They will cure Cystic Fibrosis.

"Nothing is insurmountable. Yes, you will face failures, but you run around that failure."

Erika Berg (*host*):
Perseverance is a great lesson. Many thanks to all our panelists for being with us today. It has been a delight. I learned so much and I hope our audience did as well. Goodbye everyone.

Advocacy in rare disease: Crafting the public narrative

Advocacy in rare disease is complex and challenging, but there are effective methods that advocates can use to communicate with the public. In this panel discussion, experts in communication, public relations, and influencing will discuss strategies and tactics to advance advocacy for rare disease. The discussion will explore how advocates can:

- Raise awareness on how rare disease impacts individuals and families through social media, events, press releases, storytelling, and community engagement, and by targeting to local and national media outlets
- Provide education to families, communities, schools, healthcare providers, policymakers, and the general public about rare disease diagnosis, symptoms, and treatment options
- Build relationships with stakeholders such as government officials, biotech, healthcare professionals, patient organizations, and pharmaceutical companies that can help advocacy efforts
- Lobby for policy change to improve access to health care, funding for research, access to treatments, and insurance coverage
- Create patient advocacy groups that provide a powerful grassroots platform for advocating for rare diseases.
- This poses a broader question: Just as every person is unique, could all medicines become so too?

Panelists

Mary Dunkle
National Organization for Rare Disorders, Quincy, MA

Anne Rancourt
National Institutes of Health, Bethesda, MD

Sparsh Shah
Musician, motivational speaker, philanthropist, and patient advocate, Iselin, NJ

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

The Conversation

Erika Berg (*host*):
Hello everyone and welcome to our second webinar in the 2023 Science Series on advocacy in rare disease, entitled Crafting the Narrative. *I am Erika Berg, Director and Senior Editor for Custom Publishing at* Science, *and I will be the moderator for this discussion. Today, we are going to discuss the stories we tell when it comes to rare diseases and how advocates can use words to raise awareness, provide education, build relationships, and lobby for change.*

Sparsh Shah:
It is an honor to be here among you all. My name is Sparsh Shah. I am 20 years old. I am a singer, rapper, songwriter, music producer, inspirational speaker, Guinness World Record Holder, and philanthropist, who also has osteogenesis imperfecta type VIII.

Mary Dunkle:
I am a senior advisor to the National Organization for Rare Disorders, or NORD. I have been with NORD since 1999. I originally joined as senior director of communications and for many years oversaw NORD's communications, website, publications, etc. I am now focusing on NORD's educational outreach.

Anne Rancourt:
I am the communications director at the National Institute on Drug Abuse, part of the National Institutes of Health, where I have worked for more than a decade on women's health, HIV, and drug use and addiction issues.

Erika Berg (*host*):
We will start off by talking about language. Sparsh, should we be using the term "rare disease"?

Sparsh Shah:
I think, as with anything to do with language, it has to do with context. Rare disease is no exception, especially because this topic means different things to different people. It means different things to scientists, to patients, and to communities. I feel like most times that we use the term "rare diseases", we use it in a scientific context. With that context in mind, I feel like rare disease is entirely appropriate to use because it is a rare condition and many rare diseases do leave us with some sort of functional impairment, be it physical or neurological, maybe something in between those lines, or both. The only thing I would say about the use of the term "rare disease" would be that it is probably just not best to use it anywhere where it could make someone feel like they are less than someone else just because they have a rare disease.

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Erika Berg (*host*):
Thank you. Mary or Anne, any additional comment on that?

Mary Dunkle:
Yes, I have a couple of thoughts. I think it is a really interesting question. You never want to imply that these diseases are inconsequential because they are rare. We have used slogans and campaigns over the years, such as, "Everyone knows someone with a rare disease,", because when you think of rare, it is easy to think, "Oh, that is something that hardly ever happens and it happens to somebody else, so it is sad, but it is not going to affect me." We have struggled against that and had numerous ongoing campaigns over the years.

Sparsh mentioned the scientific context and I think there is a practical reason why we would have to use something like the word "rare". This year, we are celebrating the 40th anniversary of the Orphan Drug Act, which has been incredibly impactful and important for this community. The patient advocates who founded NORD worked very hard to get this piece of legislation passed by Congress. It was signed by President Reagan in 1983 and provides financial incentives that have been incredibly important in encouraging research and development of treatments for these diseases. So, for the purpose of that legislation and to qualify for the incentives, a disease must be believed to affect fewer than 200,000 Americans.

Erika Berg (*host*):
Anne, I imagine that you think a lot about language in your line of work. Could you talk about how you decide how to describe a particular condition at the Drug and Substance Abuse Agency?

Anne Rancourt:
I think that these types of conversations are really happening across diseases and conditions. They are very often brought about by the patient community and their loved ones - people who, for many years, have had labels applied to them, scientific or medical or policy gatekeepers. Now we are in a period where we are really questioning that and in many cases, revising them to be more reflective of a person with lived experiences and perspective. I think that it is a wonderful, valuable, and important conversation worth having. The thing that I try to keep in mind as names change and issues arise, is to always keep an open mind. Language is ever evolving, in culture and across cultures.

> ***"Language is ever evolving, in culture and across cultures."***

So, as we make changes to the language that we use, it is a good opportunity to be open and reflective on the changes behind it. What is the emotion, what is the reasoning, what is the scientific accuracy behind the changing name? How can that conversation about the name itself inform the science, inform the conversation, inform policy? It can be an issue that opens up a broader conversation with a lot of benefits.

Erika Berg (*host*):
A related term that is sometimes used would be "disability". Sparsh, do you have any thoughts on whether we should be using the term "disability" when it is applied in the rare disease space?

Sparsh Shah:
Again, context is emperor. The way that I have heard this term being used in general, is like a label that has been applied to us, as Ms. Anne so beautifully said. However, the good thing is that people in marginalized groups have an amazing ability to take the labels that society places on them and then own them. For example, the LGBTQ+ community adopted the word "queer", or the Christian community adapted the word "Christian". These were all derogatory labels, and we took them and made them our own. In the same way, when you look at the very word "disabled", it is "dis-abled". It implies that, because of our functional impairments, there is something about us that makes us less than people who don't have a disability.

> ***"People in marginalized groups have an amazing ability to take the labels that society places on them and then own them."***

As a philanthropist, and through the music that I make and the speeches that I give, that is something that I really try to tell people, to break that stigma surrounding that word. I have been super blessed to be able to do all the different things that I mentioned in my introduction. It is a huge blessing to be able to live the life that I live. I really feel like this is something that I also evolved in learning. I used to tell people that God closed the door on my ability to walk, but then he opened the door to my voice for me to be able to speak and sing and all these things.

Around 2020, I was doing this scholarship essay for Lyme Connect. They were asking me about what my viewpoint is about disability. During that deep reflective period, I came to realize: is the reason I am really saying that "one door closed and one door open" because that is how I feel about myself, or is it just because it is the best way to explain my situation to people who live in a world that wasn't originally built for us? If this world was built for us, I feel like a lot more people would see it as, the way I see it: God never closed a door on me by giving me this condition. Science or nature never gave me a bad hand by giving me this genetic mutation. It is a window. It is not a door. I just started to realize that. Now, all you must do is open the window and go out. That is what I am doing.

Erika Berg (*host*):
Mary, NORD is an umbrella organization that partners with a variety of smaller patient advocacy groups. How do

communication approaches differ for an umbrella organization that is considering many different rare diseases versus a patient advocacy group that may be targeted on a single rare disease?

Mary Dunkle:
We always defer to the disease-specific organizations as the experts on their diseases. We frequently get, for instance, media inquiries seeking medical experts to speak on certain diseases or certain topics that are in the news, and we always go first to the disease-specific groups to see if one of their medical advisors would want to respond. I think there is a wonderful and unique role for umbrella organizations. I should also mention that there are organizations like NORD around the world too, and we work with them. Our role is to help to amplify the voices of the individual disease-specific patient groups by bringing them together, helping them to see our common ground, our shared interests across the spectrum of topics in public policy, research, and education. How can we work together to educate the public, medical professionals, medical students, about particular rare diseases, and rare diseases in general?

"Our role [at NORD] is to help to amplify the voices of the individual disease-specific patient groups by bringing them together, helping them to see our common ground, our shared interests across the spectrum of topics in public policy, research, and education."

There are many aspects of living with a rare disease that have many commonalities across the spectrum of diseases. NORD's slogan is "Alone we are rare, together we are strong." We try to help the people in all the individual groups find that shared experience together and figure out how best to work together. We also provide a platform to amplify their voices, and even tools like a Facebook group where the leaders of the individual patient organizations can share their experiences, ask questions of each other, figure out best practices or best ways to address certain things. I think it is a nice mix of these in many individual disease-specific groups that are doing fantastic work on behalf of their communities. Through NORD, they can come together and figure out how best to work together. Beyond that, we work closely with EURORDIS, an organization like NORD in Europe. We also helped form an organization in Australia years ago, so many other umbrella groups exist around the world.

Erika Berg (*host*):
Anne, what communication tools have you used which have worked best when applied to influential groups and high level decision makers? How can we communicate with those groups most effectively?

Anne Rancourt:
There has been so much conversation in the past 20 years about what can be done on social media and using digital tools, and all of that is incredible. I think it democratized a lot of communications, outreach, and sharing of stories which are incredibly powerful. When it comes to reaching influential groups, I think it is gone out of vogue to talk about the role of mainstream media as a really powerful communications tool, but at the end of the day, it really remains incredibly important.

Working with large media outlets, such as the New York Times, the Washington Post, the Associated Press, or broadcast news, remains essential to reaching huge groups of millions of people with one story. Working with reporters who are amazing at storytelling, at researching these extremely complex areas of disease and of science, and teasing apart those stories and the issues that matter there, is incredibly rewarding and can have a huge impact in reaching organizations and people who are really working at a high level in terms of national or state-wide reach. Getting into the daily paper really draws attention, gets an issue noticed, and can be an important first step toward a conversation on disease issues that might not have been urgently on the radar before.

"Getting into the daily paper really draws attention, gets an issue noticed, and can be an important first step toward a conversation on disease issues that might not have been urgently on the radar before."

Sparsh Shah:
As a musician and speaker trying to develop his craft, mainstream media is definitely one of the best tools that we can use to share our story. Thinking back to times when I was covered quite a lot by mainstream media, for example, for my cover of Eminem's Not Afraid, one of the main angles for press to grab on with this story was the fact that yes, it was a viral cover, but it is also a viral cover by a 12-year-old who has osteogenesis imperfecta. As a patient, I could take this one of two ways. I could either say, "Ugh, why are people trying to grab onto the disability side of things all the time?" , or, I could decide "okay, this is great".

Honestly, it is a privilege for me to be disabled, because it brought me to a much higher place in my career. I was also able to use my contact with mainstream media and all the stories that people were telling about me to say, first of all, "Yes, this is what I have, this is my condition", and bring awareness about OI. Second, it enabled me to clearly say, "No, this is not about pity or sympathy. This is about looking at me not for what I look like, but for what I can do and what I can bring to the world." I think that kind of talent, that kind of ability might perhaps be a little harder to find in people with rare disease, or it may be a little easier in some cases, but no matter what, if we can find the hidden gems in everyone and polish that coal into diamond, then it doesn't matter whether you have a rare disease or whether you are disabled. You can make an impact on the world, and that is what makes you uniquely you and that is why you belong here and you are worth it.

"No, this is not about pity or sympathy. This is about looking at me not for what I look like, but for what I can do and what I can bring to the world."

Mary Dunkle:
Just one brief follow-up thought. I think having a compelling call to action is always really helpful. We do an annual conference in the fall where we bring together leaders of patient groups, researchers, medical professionals, and government partners from the offices at NIH and FDA that deal specifically with rare diseases and orphan products. Every year, during the period of time leading up to the conference, I get so many inquiries from leaders of patient groups who see this as an opportunity to somehow catch the interest of a researcher, somebody at NIH, or somebody who might become interested in their disease. So, one year, we essentially asked, what would you want to tell the world about your disease in 200 words or less?

We invited people to submit these little vignettes and each one with a photo to go with it. We got wonderful stories and photos from people, and we put them together in a little booklet to hand out at the conference. I submitted an op-ed piece to the Wall Street Journal that they used much to our great delight. These sorts of spontaneous moments do happen, when a researcher hears or reads something like this from one of the patient groups and that light bulb goes off and he or she thinks, "oh, you know, that is similar to this other mechanism of action that I am studying". Those connections can lead to important work.

Erika Berg (*host*):
Anne, what would you say is the role of storytelling in advocacy and in general with respect to health? We can then talk about rare diseases.

Anne Rancourt:
Stories are so powerful. When you think about the role that storytelling has played throughout human history, it is the stickiest way to get something embedded in someone's brain. This is how humans have conveyed information for thousands of years. It has been written into songs, it has been written into epic poems - since Homer! This is how we teach our children what we want them to do through nursery rhymes and fairy tales. You really cannot underestimate the power of a good story, a good short to the point story. Having a succinct call to action or take away from it is incredibly valuable.

"Stories are so powerful."

I work with a lot of scientists on trying to tell a research story. There is always a push pull between wanting to share a lot of data, a lot of numbers or prevalence data, and the more human side to convey emotion. They are both important. They both serve their own role. I think that when people walk away from a conversation, if they have heard a compelling story, they are going to remember that forever. When you think about some of the most impactful conversations you have had with people, you remember the story that they told. You remember the emotions that were in it and the way that it made you feel and how you related to it. I think that people are often afraid to tell a story. It feels really colorful, imaginative. When you are talking about medicine or about science, you don't think that it is the place to be imaginative or to use a story.

"There is always a push pull between wanting to share a lot of data, a lot of numbers or prevalence data, and the more human side to convey emotion."

But it absolutely is the place, because it is how people are going to connect and how people are going to take action because they feel compelled based on the emotion that they have experienced from the story. I think that there is also a lesson to be taken from comedians. I always think of comedians when talking about training to tell these stories. Comedians don't just go out on stage and do a standup routine. They hone it, telling jokes, telling their stories over and over again at comedy clubs until they really have it packaged in exactly the right way so that it hits their audience, and they get the response that they are looking for - in their case, obviously laughter. That is part of storytelling - figuring out what your story is, how you want to tell it, what are the details that people really respond to. Watching your audience as you tell the story and working on it over and over again until you come out with the best way of telling that story and then repeating it over and over again.

Mary Dunkle:
I agree with everything Anne said, and I wonder how many lives Sparsh has touched with the stories that he has told through his walks and videos. I think with rare diseases, it is even more important than with other kinds of health-related topics, because there are thousands of these diseases, anywhere from 7 to 10,000 or more, depending on whether you are counting the various subtypes and that sort of thing. Many of them have very strange long names. It is hard for people to remember. They may sound foreign, but having a real person who is living with that disease share his or her story in a positive way on the realities of living with that disease on a daily basis can mobilize people to understand and want to help and support.

I will just add that we also see an incredible bump in traffic on our website or just the general public conversation when a celebrity or some well-known person makes public that he or she is affected by a rare condition. Some months ago, the singer Celine Dion said that she has stiff person syndrome, and that is a condition that you hear very little about. My goodness, we got a huge bump in traffic to our website after she made that announcement. People were going directly to our report on stiff person syndrome. I know that the organization specifically for that community was getting tons of media inquiries because we asked them if they wanted to comment or have one of their medical experts comment and they responded, "It is wonderful, but we are swamped".

"Having a real person who is living with that disease share his or her story in a positive way on the realities of living with that disease on a daily basis can mobilize people to understand and want to help and support… We also see an incredible bump in traffic on our website or just the general public conversation when a celebrity or some well-known person makes public that he or she is affected by a rare condition."

At our 40th anniversary dinner, at the National Portrait Gallery in Washington, Peter Alexander of NBC News served as MC because his sister has a rare condition known as Usher Syndrome. He has actually done a wonderful job of promoting awareness of that condition. Anytime somebody like that makes some sort of public comment on his or her experiences, it reaches a lot of people and it is very helpful to the community.

Erika Berg (*host*):

In cases where celebrities don't have a personal connection with rare diseases, how can we influence the influencers, politicians, public figures? How do we raise awareness and influence them to get involved?

Mary Dunkle:

I think collaboration is key. There is a wonderful community of people coming from different perspectives who are interested in rare diseases for various reasons. This includes the leaders of the patient advocacy groups, but also medical professionals. The doctors, who choose to devote their careers to focusing on rare diseases, really are a special breed of people: they are very supportive of patient organizations and patient communities. There have been some wonderful things written and said in presentations in recent years. I am thinking of one doctor in particular at CDC, who has been very active in exploring this idea of rare diseases as a public health concern. Even if we use the word "rare", we need to get away from this idea that it is just something that happens infrequently to somebody else.

Bringing together this community of people who are either treating patients or doing research in the pharmaceutical industry developing products for rare diseases, enables to show a united front and to work together in getting our messages out there. In my experience, the public officials really want to do a good job. They must work within certain budgets. They have certain limitations and constraints. But if we do our homework, if we pull the community together and make a good case to them, I think they do listen.

"In my experience, the public officials really want to do a good job…. They have certain limitations and constraints. But if we do our homework, if we pull the community together and make a good case to them, I think they do listen."

Sparsh Shah:

This makes me think of my work as a philanthropist. I have been blessed to help serve people who are less privileged than me, or just people who just have it worse than I do, especially in infrastructure of socio-economic terms. In the rare disease/disability sector, I am a youth ambassador and advocate for some of these organizations that I work with. One of them is the Voice of Specially Abled People or VOSAP.

I mention them because it goes exactly with this topic. There are three main prongs through which we help elevate the lives of people with disabilities or as we call them, specially-abled people. First, being grassroots, like a mobile app where people can just sign up, volunteer, and use the map we have, to go to any public place and take a picture and rate it for accessibility. The rating is not just in terms of whether the place has ramp for people in wheelchairs, but also whether the elevators have braille on them so blind people can read them, or whether there are people available to help guide people who are hard of hearing, or tour guides.

Second, there is Academia: for example, we have been starting research internships with college students. It is something that I want be a part of one day. I got to speak at one of their summer internship conferences to the students. We do lots of research on every single aspect of the issues surrounding people who are differently abled in terms of policy, data... It is all about data-driven research to go to the top level - that is, politicians or governments. We have been working quite a lot with the government of India and their legislation to change in language regarding people who are differently abled. We are one of the organizations that helped to foster that change in language and in legislation, bringing more accessibility in terms of infrastructure to, for example, government buildings, or changing the word "viklang" to "divyang" in current public discourse in India. Also, we all may have heard of ADA 2.0? That is something that we are also trying to work on recently in America, by talking to legislators about getting that passed because that is going to bring a lot of benefit in terms of government, infrastructure, and everything for people who are differently abled.

Erika Berg (*host*):

Anne, do you have a public campaign advocacy success story from your experience that you could share with us, that we could benefit from hearing about?

Anne Rancourt:

In the spirit of storytelling and the power of stories, one of the most famous stories of advocacy and NIH working together was way before my time, in the late 1980s. It is a story that sticks with us: the story of AIDS activists that came to the NIH campus to protest against policies that were keeping them from getting, lifesaving drugs outside of the auspices of a clinical trial. This was before Instagram, before we were all trying to create these incredible visuals that you could photograph. They held an incredibly visual, theatric, and passionate protest that drew a ton of media attention, but also the attention of NIH leaders, who I think finally resonated with what the advocates were asking for and invited them in and sat down with them. That began a very productive conversation.

The advocates were, like so many disease advocates, incredibly well versed in science. They were not themselves scientists or having scientific training, but they really wanted to learn, to have that productive conversation. What I think is so interesting about that story is that there was this incredibly pivotal point where there had to be a change from the theatrical protest. Certainly, those continued and needed to happen to continue the pressure, but coming to sit down together in a room and begin that conversation is a really a pivotal point in the process of advocacy. It was important on the government side as well, as they heard that advocacy, were receptive to it and brought it to the table. For AIDS, for HIV, it resulted in a great change to clinical trial policy. People were able to gain access to the medications that could help save their lives.

There was this mutuality to coming to that point and recognizing when it was time to sit down together, how to have that conversation, knowing both sides, so that they continue to each have their own perspectives, their own agenda moving forward. But how can we begin to do this together? There certainly needs to be an openness on both sides to finding that point and knowing that for progress, that point must be realized. So, that is something that I think is a great example to keep in mind. As a public official, that is one of the stories that is very important in our organizational culture at NIH. That was really one of the most impactful times that it became so clear that people with lived experience must be involved in the research process, in setting the agenda, designing the research, and having a voice throughout the process.

"It became so clear that people with lived experience must be involved in the research process, in setting the agenda, designing the research, and having a voice throughout the process."

Erika Berg (*host*):

Thank you. Anyone else has a success story they would like to share?

Mary Dunkle:

One that comes to mind is Rare Disease Day. In 2008, I was in Europe for a conference, and I remember coming back to my hotel room that evening and just flipped on the TV and suddenly became aware that there were stories about people with rare diseases on TV. That was amazing to me, so when I got back home to the states, I heard from our friends at EURORDIS, the European umbrella organization. It turned out that it was the first ever Rare Disease Day that they had launched. They did it purely to promote awareness and to educate, and it was a pretty successful first day! They then asked NORD to bring it to the US the next year in 2009, which we did. It takes place on the last day of February each year, because the first one was on February 29th, the rarest day.

It has grown since. I must admit that my initial reaction was, "Well, that is nice, but there are so many awareness days, it passes. I don't know if we want to add one more." I kind of reluctantly got dragged into doing it, and it has turned out to be hugely beneficial for the community. It has grown incredibly over the years. If you are anywhere near social media beginning anytime in February and culminating on that last day, you will just see tons of posts, stories, photos, special events taking place, and media stories. NIH hosts a wonderful Rare Disease Day event each year now. NORD creates resources for teachers to use in the classroom and local families who want to educate students can work with their teacher to go into the school on that day. All sorts of things are happening, and it has really been huge.

Sparsh Shah:

I wanted very quickly share a success story. VOSAP has done something really cool during the pandemic in 2020. We called it the Art from Heart contest. I think it ties into what Ms. Mary and Ms. Anne were saying about the colorful theatrical way of telling a story. We had a contest and invited people from all over the world. This was the first international art contest, specifically on the theme of disability. We had people create visual art that deals with the anxieties, hopes, fears or joys of people who are specially abled. I think approximately 53 countries were represented, as well as at least a hundred, or maybe 200 cities all over the world. There were hundreds of artists who applied. I remember when it was time for the annual gala that year, we were declaring all the winners and just looking at the art, it was like, wow. It was so amazing, because a lot of the people submitting art were people with these lived experiences. So, that art flowed straight from their hearts and, being an artist myself, I can relate to that. The power of storytelling is in the places I think that we can least expect it. I think that is where the most powerful stories can be told. It really shows how important it is to get stories from, as John Legend would say, ordinary people living with rare disease or any other health related or any other issue of importance.

Erika Berg (*host*):

Sparsh, what are some best practices for using social media or other engagement tools for raising awareness?

Sparsh Shah:

This is a great question, and to be very honest with you, I feel like this is something that I am still learning, because I am still a growing and developing influencer. I am not just doing this just for advocacy, but also for my career. One, I want to talk about something totally unique. I think one interesting thing that I would love to see more, and I would love to do more as well, as an influencer, is to think from the perspective of modern social media trends, not just specifically in advocacy, but social media trends in general. Think of popular songs on TikTok. Now imagine taking those wildly popular trends or creating those popular trends if you are someone in the music space like me who is trying to make their songs trend worthy, and pairing it with a story that can help advocate for rare disease, pairing it with lived experience.

For example, I recently released a song called, 'This Is Me, The Rap Prince.' The first verse is a mini autobiography. The second verse is my vision statement to the world. In the first song, I am talking about my whole life and how the doctors gave me 48

hours to live. I had 35 to 40 broken bones coming out of the womb - those kinds of things, right? In a sense, I am indirectly telling people about OI and what I go through as a person with OI.

One thing I did, was that I took particular lines, such as "I was bound to die, ain't no lie. Parents cried, life hung, a thread of silk. But I survived that trial, the first of many cases." or "I survived that trial," and the musician in me, was like, "Repeat that." "I survived that and that." Every time, it repeats, it switches images. I just made a bunch of images that tell that story of my life. I haven't seen it yet, but would love to see people using that sound, making the lyrics universal. Now, everyone can use that sound, or that template, to tell their story of the trials that they survived in life, whether they have a rare disease or not.

That can start an even bigger conversation because the whole context of that verse was what made me different and why I almost wasn't here to be here today. That is a very specific example, but I think it would be so cool to continue using popular trends like that or create trends like that, that appeal to the masses in a very natural way.

Anne Rancourt:
I will leave the best practices to Sparsh because I don't think there is anything competing with that. The creativity there is just so wonderful. The greatest part of social media is getting to see that from people. From the boring organizational end, I don't think people usually look to government agencies as the bulwark of creativity on social media or anything, but that is okay. I do think that agencies such as the NIH, and other large organizations, that are on social media but aren't out there doing these creative things and grassroots campaigns, are really open to being a part of the conversation or being involved or helping in some appropriate way for their accounts and for what they represent.

"Agencies such as the NIH, and other large organizations, that are on social media but aren't out there doing these creative things and grassroots campaigns, are really open to being a part of the conversation or being involved or helping in some appropriate way for their accounts and for what they represent."

At the NIH, it is about communicating the science, that is our mission space. I think that communications offices are often staffed with people who want to be a part of these creative endeavors in the right way, so they are very open to being asked to collaborate or to being approached in some way. So, my advice is to be always never afraid to reach out with an email to communications offices and say, "Hey, I am going to do this. If it is something you would be interested in, let me know, we can discuss." It is not always a fit. Obviously, I can't speak for every communications office if you will hear back or not, but I think, nothing ventured, nothing gained. It is always a really great way to start a relationship or a dialogue about messages where you have a mutual interest.

Mary Dunkle:
Anne was being modest, but I think it has been an incredible help to us to have the information that NIH provides about diseases. I think it would be impossible to overstate the impact of the internet and social media on people with rare diseases. I recall hearing NORD's founder and first president talk about how for many years, when a story would come out, for instance, in Reader's Digest or some widely read publication, and there would just be bags of letters coming into NORD from people across the country who were thrilled to find out that there was an organization that existed that might help them and had no other way to communicate. They were seeking to connect with other people with their disease and that sort of thing.

Obviously, social media has completely changed that. While we always remind people to be careful of the sources to make sure they are getting information from reliable sources, the internet has been truly wonderful in general for those folks. We are often contacted by people who, for instance, have a child who has just been diagnosed with a condition that maybe there are a dozen children around the world known to have the condition, and for them to be able to connect with other families, share information and resources, feel like there is somebody they can talk to and be heard, that is hugely important.

Erika Berg (*host*):
Thank you so much. Unfortunately, we will have to stop there. Many, many thanks to our panelists for being with us today. It has been a delight talking with you all. Goodbye everyone.

Advocacy in rare disease: Closing the funding gap

Securing funding for healthcare research is rarely easy, but it's particularly challenging for rare diseases. Each of these, by definition, affects a small portion of the population, making it easy for funders to overlook rare disease research. However, addressing the funding gap is crucial, because collectively rare diseases impact the lives of millions of individuals and their loved ones worldwide. Furthermore, research into rare diseases has the potential to drive forward our understanding of other more common diseases and of human biology overall. To begin with, compelling governments to expand their support of research and development in rare diseases is an advocacy priority. In addition to traditional grants, government funding could go to research institutions and organizations dedicated to studying rare diseases. Additionally, governments can create incentive programs to encourage pharmaceutical companies to invest in rare disease drug development by providing grants, tax breaks, or extended exclusivity periods.

Public–private partnerships also play a key role in closing the funding gap. They can facilitate knowledge-sharing, resource-pooling, and joint efforts toward finding effective treatments and cures. Advocating for international cooperation is another key strategy. Establishing global networks and collaborations that include venture capitalists and banks can facilitate the sharing of research findings, best practices, and funding opportunities. International funding bodies and foundations can also prioritize rare disease research and encourage collaboration across borders.

In this panel discussion, participants will:

- Learn how closing the funding gap in rare diseases requires a multi-faceted approach
- Hear strategies for increasing government funding, collaboration among stakeholders, and international cooperation
- Get information on how rare disease research can benefit not only those with rare diseases and their communities, but the wider world as well.

Panelists

Daria Julkowska, Ph.D.
Inserm, Paris, France

Christine Mueller, D.O.
US Food and Drug Administration, Silver Spring, MD

Ford Runge, Ph.D.
University of Minnesota, St. Paul, MN

Julie Saba, M.D., Ph.D.
University of California, San Francisco, CA

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

The Conversation

Erica Berg (*host*):
Hello everyone and welcome to the third webinar in our 2023 Science Series on advocacy in rare disease, entitled Closing the Funding Gap. I am Erica Berg, director and senior editor for Custom Publishing at Science and I will be the moderator for this discussion. In this panel discussion, we are going to take a deep dive into the thorny issue of funding in rare diseases.

Julie Saba:
I am Julie Saba. I am a Pediatric Oncologist and professor of pediatrics at UCSF, University of California, San Francisco. My career began in my fellowship years. At the same time, I was doing graduate work trying to find new genes involved in cancer. I honed in on an obscure pathway called the Sphingolipid Metabolic Pathway and cloned some genes in that pathway. Jump forward 30 years, and just about 5 years ago, my colleagues and I discovered that a mutation in one of those genes causes a rare disease. So, I have recently shifted my focus to try to develop therapeutics and a better understanding of the pathogenesis of this disease.

Christine Meuller:
I am a medical officer in the Office of Orphan Products Development at the US Food and Drug Administration. I work primarily as a project officer on our grants programs for rare diseases. I am a Clinical Geneticist by training and I have also worked at the National Cancer Institute on research for rare cancer syndromes, as well as the Common Fund at the NIH.

Daria Julkowska:
I work at the National Institute of Health and Medical Research in France. I have a PhD in Molecular Biology. I have been involved in rare diseases for the past 13 years. Since 2019, I coordinate a big European program, which is called the European Joint Program on Rare Diseases, that brings together over 130 institutions from 35 countries from Europe and beyond that are working together to create an ecosystem that supports rare disease research. I am also coordinating the scientific secretariat of the International Rare Disease Research Consortium. So, I work in rare diseases with a very passionate community and I am very happy to be here.

Ford Runge:
I am a McKnight Professor of Applied Economics and Law at the University of Minnesota. My connection to these issues is quite personal. I have a daughter who was diagnosed with Smith-Magenis Syndrome, which is a rare disease, and has a lupus diagnosis. I have worked on this issue with my son who is at the Biomedical Research and Development Authority in Washington. For over 20 years, I have been associated in obesity and thermogenesis research with Dr. James Levine, who is now at the Fondation Ipsen in Paris. So, my interest is in the application of economics to the challenge of rare diseases.

Erica Berg (*host*):
Julie, this webinar is called Advocacy in Rare Disease: Closing the Funding Gap. Is there a funding gap?

Julie Saba:
That is an easy question to answer. Yes, there is a funding gap. I think it is understood that there are many millions of people affected by rare diseases, but each one represents a small number relative to the more common diseases of aging that our society faces. It is a challenge to convince society and the funding agencies to invest in the development of therapeutics, diagnostics, and everything else that is needed to advance the health of individuals with rare diseases. On one end of the spectrum, there is the very early basic science recognition of the genetic cause of a disease, which is a very exciting prospect and gathers a lot of attention and can be funded.

> ***"It is a challenge to convince society and the funding agencies to invest in the development of therapeutics, diagnostics, and everything else that is needed to advance the health of individuals with rare diseases."***

On the other end of the spectrum is the development of therapeutics by pharma companies, where things are already well developed. However, there is a space in between where individuals and groups have to be working to understand the mechanism of the disease, the methods of diagnostic discovery, development of biomarkers, the finding of patients, and the relevance to more common diseases because monogenic diseases can obviously indicate the role of a pathway in more common diseases, which garners more attention. So, there are a lot of different reasons why there is a funding gap, but yes, here is one.

Erica Berg (*host*):
Ford, I suppose you already mentioned your personal connection to rare disease, but what drew you into the study of rare disease as an economist? How did you find your role there? What role does an economist have in the rare disease space?

Ford Runge:
I teach an advanced PhD level course at the University of Minnesota in Applied Economics. I have several students who come in from the health sciences PhD to take my course. So, there is quite an interaction with that group. Because I had familiarity with some of the work of Fondation Ipsen, I enlisted some students in the PhD program to begin to help see if we could apply basic economic reasoning to some of the problems of rare diseases. There is a pretty well-established tradition in plant breeding research looking at the way in which research in one area spills over into research in others. So, I began to discuss with my students whether we could apply some of the basic principles of Economics analysis which looks at spillover effects.

Economists typically refer to them, somewhat obscurely, as externalities, to see whether we could begin to cluster rare diseases in ways that would facilitate insight from one rare disease to another or from one rare disease into more common diseases. The general implication, if we can document these spillover effects, is that we are under investing in rare diseases because the benefits of insight at the level of treatment, at the level of research design, or at the level of the development of networks to share information on rare diseases, all implies that the returns to this investigation are larger than appear at first sight. So, this goes directly to the first question you raised about funding gaps and under investment. That is my take on this. It is very much a perspective from the point of view of Economics. I defer entirely on the matter of science to my panel mates.

Erica Berg (*host*):
Thank you, Ford. Does anyone else have a comment? Have you heard of the term "spillover effects" in your own work?

Daria Julkowska:
I think that the problem with rare diseases is that we need to find the arguments for rare diseases to be funded. Of course, one of those arguments is that rare diseases have impact or are kind of helping to understand better the more common diseases. However, I would say it is difficult to always use this kind of arguments to obtain funding, especially, for example, in basic research where you have a project where you must justify why you are working on a disease for which there are, for example, only ten patients all over the world. Obviously, it is not easy.

> ***"We need to find the arguments for rare diseases to be funded."***

My question or comments to Ford would be: how we can also stimulate the collaboration between the scientists in Economics and the scientists that are working, for example, from the biology or medical perspective? I think this linkage is still not sufficiently established, while the impact of rare diseases, or the burden of rare diseases, or the economic positive impact of the research on rare diseases, is still lacking some more concrete numbers. This is obviously connected to the data that can be brought in by other types of researchers.

> ***"How we can also stimulate the collaboration between the scientists in Economics and the scientists that are working, for example, from the biology or medical perspective?"***

Erica Berg (*host*):
Ford, how can we connect biologists and biosciences with economists in the rare disease space more effectively? You were

saying some of your students are health students, is that right?

Ford Runge:
It is important to encourage funding agencies to think about developing interdisciplinary teams that include analysts from economics and from finance. One of the interesting questions that rare diseases pose is: if a potential investor is looking at the research programs in this area, how can we develop clusters of activity and portfolios in which the likelihood of spillover from one disease to another or to common diseases is greater? We have roughly 7,000 rare diseases out there, but within that 7,000, surely there are clusters of diseases that have an affinity for one another, such as applications of artificial intelligence and other statistical methods that can be used to ferret out what these potential relationships are, and to create investment portfolios that might be attractive to venture capitalists. So, there is both an economic analysis and statistical component to this. There is also an effort to reach out to the investment community. All of these types of activities and people need to be better represented, it seems to me, in the enterprise of rare disease research.

"One of the interesting questions that rare diseases pose is: if a potential investor is looking at the research programs in this area, how can we develop clusters of activity and portfolios in which the likelihood of spillover from one disease to another or to common diseases is greater?"

Julie Saba:
I think there are some natural affinities from a scientific and anatomical viewpoint. In the Sphingolipid field, there are many commonalities within the biochemical pathway for the many different new diseases that are being discovered by next generation sequencing in that pathway. For example, the lysosomal storage diseases, Tay-Sachs, Sandhoff, Fabry, Farber, Gaucher, are all related diseases and they have a natural affinity for one another because they are all affected by enzymes in the lysosome. There are other whole groups of diseases that are affecting the central nervous system, and there are so many genes that are poorly understood, but are known to be linked to developmental diseases, that if we look anatomically at the gene expression in the brain, different anatomical locations, we could see these natural clusters of scientific activity and sharing of information. One of the problems is that it takes a champion or a couple of champions, either in the scientific realm or in the patient realm, to be able to organize all of this and create enough of a systematic organization within multiple institutions to be able to vie for funding as a cohort. That is challenging. But there is a path. That is where I would see assistance being very helpful.

Ford Runge:
If I might return just for a minute to the conceptual perspective on this, in plant breeding research where we have seen spillover effects from research programs to other research programs, one of the things that was quickly realized is that research tends to spillover effectively in Agro-ecological zones in which various plant varieties live. So, in a rough kind of way, one question to ask here is: within the large set of rare diseases, where are the affinities that are effectively analogs to Agro-ecological zones, in which the molecular characteristics of the diseases are shared? Again, Julie, I defer to you on answering questions like that.

Erica Berg (*host*):
Christine, what is the role of the government in funding rare disease research? Could you tell us a little bit about the Orphan Drug Funding Program and the gap it fills?

Christine Meuller:
Just to go back to the previous discussion, one of our initiatives is to focus on innovative and efficient trial design. So, we have on the farther end of the discussion added some extra funds to our funding opportunities for folks that are addressing those challenges, because we recognize there are shared molecular etiologies and pathophysiologies in diseases, and collaboration is important, and extra funding is sometimes necessary for those projects. In general, the mission of the Office of Orphan Products Development at FDA that I work in, is the evaluation and development of products, such as medical devices, drugs, biologics, specifically for rare diseases. We have several programs that provide incentives for rare disease drug development. The grants program was funded beginning in 1983 under the Orphan Drug Act. Again, we provide funding specifically for rare diseases. With the over 7,000 rare diseases that are known, there are only about a few hundred that have treatments at this point. So, more than 90% of our diseases still don't have treatment.

"We have several programs that provide incentives for rare disease drug development. The grants program was funded beginning in 1983 under the Orphan Drug Act. Again, we provide funding specifically for rare diseases. With the over 7,000 rare diseases that are known, there are only about a few hundred that have treatments at this point. So, more than 90% of our diseases still don't have treatment."

Besides our office, there are our sister agencies, the National Institutes of Health, the Centers for Disease Control and Prevention, and even the Department of Defense Fund for Disease Research, that tend to fund research more in the basic and translational, sometimes clinical trial realm. We all also support public-private partnerships that play a role in funding. However, there is still a large need remaining for rare disease treatments. Our office has primarily funded a clinical trials grants program and a natural history program. We have about $19 million a year to do so. We fund about 60-80 ongoing grants at a time. We have supported product development for over 80 products and 90 indications for rare diseases. We are funding mostly small companies, academia, and we have also, like I said, more recently, looked at things that have promoted those 80 products that have been developed.

Those have primarily been collaborations with patient advoca-

cy groups, industry, and academia. So, we have added those sorts of aspects of study design into our scoring criteria. We also fund trials that support publications or clinical guideline changes. I think we are unique in that we also build on our OOPD staff and our other FDA regulatory staff in providing input onto the trials that we fund. So that is a little bit different than the other government agencies that are funding clinical trials and for rare disease research in general.

Erica Berg (*host*):

Thank you so much for that overview. The FDA is obviously a US-based organization. Daria, could you talk a little bit from a global perspective? Are there regional differences in the funding gap and funding opportunities globally?

Daria Julkowska:

Yes, clearly, there are some differences, but also, luckily, some synergies. I think that it is very important to try to build more and more bridges at the international scale. From the European perspective, and zooming a little bit into Europe, we not only have the challenge of rare diseases having few patients being scattered all over Europe, but also the fact that we have 27 countries that are part of the European Union. As you can imagine at the scale of a small country, having a dedicated rare disease research program is something which is extremely rare. So, the only way of doing things is to work together. This is something that has been done since over 20 years.

"The European perspective, and zooming a little bit into Europe, we not only have the challenge of rare diseases having few patients being scattered all over Europe, but also the fact that we have 27 countries that are part of the European Union. As you can imagine at the scale of a small country, having a dedicated rare disease research program is something which is extremely rare. So, the only way of doing things is to work together."

In Europe, we also have, for example, the multinational research funding program that allows the funding of the multinational research projects, that combine different expertise and teams from different countries, allowing not only knowledge sharing, but also to bring together all the expertise available. So, this is something very important and this is the way Europe works. At the global scale, when thinking through the perspective of the International Rare Disease Research Consortium, we can clearly see that there are differences in different parts of the world. For example, in low and middle-income countries, one of the main problems or challenges in relation to rare diseases is the fact that rare diseases compete with the more common diseases – but these common diseases can be HIV in Africa or in India, or malaria in other regions.

"At the global scale, when thinking through the perspective of the International Rare Disease Research Consortium, we can clearly see that there are differences in different parts of the world. For example, in low and middle-income countries, one of the main problems or challenges in relation to rare diseases is the fact that rare diseases compete with the more common diseases – but these common diseases can be HIV in Africa or in India, or malaria in other regions."

So, pulling the resources for the rare diseases is also still very challenging in other parts of the world. So, there are clearly different models in terms of funding. In Europe, the collaborative model is the primary way of working together, because doing it at smaller scale doesn't make sense.

"In Europe, the collaborative model that is the primary way of working together, because doing it at smaller scale doesn't make sense."

Erica Berg (*host*):

Julie, how do we get funding? Can you tell us a little bit about your experience obtaining funding for gene therapies in rare disease, and what you have learned?

Julie Saba:

I have had successes, and they have come from a variety of ways. I think I would start back at the beginning where I was not successful. One of the avenues that I took was to go to the industry, because I was really dealing with the therapeutic approach – although I have been spending my life in basic science, I just realized that, with my expertise, I was the one person who might be able to help the families and the children with this particular disease. I just turned my attention strictly to therapeutics. But I was told very quickly, "You need to find more patients, or you need an expansion indication." That was helpful advice. We conducted a prevalence estimate study looking for the worldwide prevalence of this disease, at least theoretically based on the presence of the mutant variance of this gene in healthy populations in which we can calculate that.

That brought us from less than 100 patients known in the world to at least 12,000 - and that is probably a very conservative estimate. Just having that number is helpful in every grant application that I write, because numbers mean something. Your reviewers, even though NIH has strict policy not to eliminate or not to base scores on how common a disease is, but it is an implicit bias, I am afraid, in the evaluation of all grants. So, one must do a very good job of making the case. The expansion indication is another way of connecting the observation of the pathophysiology of this disease to more common diseases. In our case, we connected the fibrotic kidney disease to lung fibrosis, which is a complication of COVID and other coronavirus infections.

"Just having that [prevalence] number is helpful in every grant application that I write, because numbers mean something…. So, one must do a very good job of making the case…. The expansion indication is another way of connecting the observation of the pathophysiology of this disease to more common diseases."

So it was a timely expansion indication that we put forth. We have been able to get funding now for all these different expansion indications and for our main projects, in large part because of accomplishing those goals of increasing the significance of our disease. That is in short some of the successes that I have had. I also think that there are so many things that are required in having a clinical trial for a rare disease. Biomarker development is one that we have been particularly interested in. Finding a biological endpoint or something that can be measured in a blood sample is another area that can be very useful for many diseases. So, I have been very successful in getting funding for the biomarker projects that we have.

"Finding a biological endpoint or something that can be measured in a blood sample is another area that can be very useful for many diseases."

Erica Berg (*host*):

Daria, could you tell us anything about some innovative funding models or mechanisms that have been successful in supporting rare disease research beyond traditional grant funding? Are there more innovative models for securing funding in the rare disease space that you can talk about?

Daria Julkowska:

Models like crowdfunding exist in the rare disease space but also more generally. There is quite a lot of innovation in approaching more traditional government related grants. For example, we are to move away from traditional funding based on scientific excellence - it doesn't mean that it does not count - to start expanding the way the funders view the funding model, especially in the space of rare diseases.

For example, we have managed to successfully secure to also provide the funding for the patient organizations in our funded research projects. This is to make sure that they can participate in research projects and that they can also be one of the drivers of the research project. They become one of the selection criteria of the project. At the beginning, it was only the criterion of the selection, but there was no funding for them. We have now moved from criterion for selection to also securing the funding, because the patient organizations were telling us, "It is great that you want us to participate everywhere, but actually we do not have any budgets to be able to participate." This is one of the things that we have implemented to make sure that those projects are more patient-need driven. So, together with the funders and patient organizations, we publish, for example, the guidelines for the researchers or how to involve patients in the research projects.

Other things are being done. For example, we make sure that all this public funding that we are investing in rare disease research is not being lost. I am not saying that the researchers are not doing a good job, but honestly, I am not really sure that your approach, or your way of thinking, Julie, is something which is very common, especially when you come from this kind of basic research area, "Okay, I am doing something that at the end may produce a specific result that is going to have an impact or can lead to a therapy and so on."

Also, obviously, we do not want to put all the burden on the researchers. They can do their research and they should do their research, without necessarily being the entrepreneur and regulatory specialist and so on. So, the other thing that we are implementing is the so-called mentoring of the research project. So, during the application, we allow the researchers to have the kind of mentoring which provides access to the specific expertise, for example, from the industry, from the regulatory, from the ethics, to make sure that they can improve their project. So, when the applications go through, they have a higher chance not only to be funded, but also to have results translatable into more meaningful results. We are also supporting them to, for example, find the follow-on funding. These are the things that we are trying to implement to have a more comprehensive ecosystem around the funding of rare diseases.

"We allow the researchers to have the kind of mentoring which provides access to the specific expertise, for example, from the industry, from the regulatory, from the ethics, to make sure that they can improve their project."

Julie Saba:

I really appreciate what you said Daria, and I failed to mention some of the initiatives that I think are very helpful. I have been fortunate to have funding from the California Institute of Regenerative Medicine. Because they are so focused on cures using gene therapy, gene editing, and cell therapy, they don't really care whether it is a rare disease or not. So, having a focus on a cure, developing a cure has been very helpful and they have been very supportive. There is a program at NIH, National Heart, Lung and Blood Institute called the Catalyze Program, which is also focused on taking basic science observations and discoveries and pushing them towards therapeutics. So, I think that that transitional phase is very important. I am also a participant of a program called Nucleate, which is actually designed to teach basic scientists like me about startups. And it gives you an important perspective on exactly what Daria was talking about: it is fine to have a basic science discovery, but what is required at the regulatory level? What is required to have a successful transition into a viable therapeutic? So, I agree that this is a really important area.

Christine Meuller:
One of the needs in the rare disease space is really the unknown natural history data in a lot of rare diseases towards being able to develop treatments for them. So, we fund natural history studies for rare diseases specifically, which not a lot of folks do. We also fund patient advocacy organizations, not just industry or academia, because we know that some of those groups really have a lot of knowledge about their diseases and are relatively active. We support collaborations through our scoring criteria as well as, one of our scoring criteria is different than NIH is specifically patient input. So, we feel that that is really an innovative aspect of our RFAs, our funding opportunities.

"One of the needs in the rare disease space is really the unknown natural history data in a lot of rare diseases towards being able to develop treatments for them."

We also include patient representatives in our reviews and provide them a chance to provide input prior to any funding of the grants that we plan to fund as well. It is because we feel like that is very helpful in moving development towards what they think is a benefit to them in terms of treatment or potentially a risk. So, I think those are important in this space, because as the US Orphan Drug Act defined rare diseases as less than 200,000, and, as Julie said, those are very small patient groups to even complete trials. So, we have seen in our programs in the past some studies that just get stuck because they can't enroll patients, because there hasn't been patient input on trial design, or there is not a well-known natural history, because patients haven't been involved in natural history studies.

Erica Berg (*host*):
What strategies can advocates or rare disease advocacy organizations use to raise public awareness, engage communities or communicate with your office in supporting rare disease funding?

Christine Meuller:
Providing input when they are asked for trial designs, encouraging enrollment in trials that they believe may be beneficial to their groups, advertising... We have a rare disease day that we support every year which tends to be primarily focused on patient advocacy and us communicating with patient organizations on how the FDA works, and how they can help us… That is one of the ways I think that is really helpful for patients to understand the FDA and get involved with us.

Julie Saba:
There is a wonderful book that was recently published called We The Scientists, that is a wonderful read about the NPC1 families and their organization, and how they interacted with the FDA and tried to get new therapeutics. It is a small book, but it is very inspiring.

Ford Runge:
One of the things that we are talking over here is that not all networks of patients and researchers and agencies are created equal. In the specific instance that I am most familiar with, my daughter's disability, Smith-Magenis syndrome, which is a microdeletion, the 17th chromosome, Ann Smith, for whom the syndrome is named at NIH, has built what I think may be a kind of model network in that respect. I think other people who are working on networks can benefit by seeing which networks for which rare diseases have been most successful. So, we can think about networks as a unit of analysis in advancing understanding and funding for rare diseases.

"So, we can think about networks as a unit of analysis in advancing understanding and funding for rare diseases."

Daria Julkowska:
I fully agree with what you say Ford. As mentioned by Christine, not only about 90% to 95% of rare diseases do not have effective treatment, but they do not even have any kind of research activity, so they are really underserved. So, building networks is something which is crucial as a starting point. On our side, we are providing a small funding, like only €30,000, for what we call networking. It is not really about research, but it is about building networks or expanding networks or sharing knowledge. We have implemented this several years ago, and we have noticed that it is very successful and that this is something that we can use to help building new networks around rare diseases for which nothing is happening yet and for which the patient organization or a group of patients are not yet organized yet into a specific patient organization, but would like to start to be connected to researchers.

Also, there are some other approaches, such as trying to find commonalities. We also know that this is something that is part of the business model or funding model for rare diseases. Having those commonalities, such as, shared molecular etiology, is something that can be very helpful when thinking about addressing the potential investors. So yes, helping patient communities to come together and helping them also from the scientific perspective is very important. I hope that by bringing those networks can help to address those 95% of still underserved rare diseases.

"Having those commonalities, such as shared molecular etiology, is something that can be very helpful when thinking about addressing the potential investors. So yes, helping patients communities to come together and helping them also from the scientific perspective is very important. I hope that by bringing those networks can help to address those 95% of still underserved rare diseases."

One very interesting initiative is the Chan Zuckerberg Initiative that you may know about. They have taken this perspective from the

other way around. They decided to finance patient organizations that want to build research projects. So, patient organizations are the drivers for the research projects. This model is also very interesting in terms of approaching the rare disease research from the heart of the need of the patients.

Erica Berg (*host*):
Julie, what role can crowdfunding on social media platforms play in trying to close the funding gap for some of these underserved rare diseases?

Julie Saba:
I haven't personally explored crowdfunding and my disease of interest did not have an advocacy group. I worked with one parent and one patient and created one. We have a website and we are just now trying to amplify our signal on Twitter and other social media tools available for us. So, I am in an early stage of dealing with that. I have too many things in terms of basic science and translation to try to do it myself, but my students are trying to help. I think that one of the great models is the Cystic Fibrosis Foundation. In terms of their awareness raising, they have been a very well-organized group but they made the decision at some point to partner with the companies that they funded and received some of the financial benefit of a drug that was therapeutically successful in one version of cystic fibrosis for one mutation. They used the funds that came back from that success to expand their organization, and that enabled them to hire people who could do all the outreach and awareness raising at a much higher level. So, their whole organization and its success at fundraising and awareness raising has been expanded exponentially. I think that is a very good example of a very practical way that advocacy organizations can leverage their power to advance awareness of their disease.

Erica Berg (*host*):
Yes, that is a great example. Anyone else have experience or observed any successes with crowdfunding or social media use with raising funding that they would like to share?

Christine Meuller:
I have seen not necessarily raising funding, but the use of social media platforms for enrolling or finding patients early on for our natural history studies or doing brief surveys. I am sure there is a little bit of weariness about private health information in those spaces, but they are a great source for finding patients and letting them know about trials that they would potentially be used for.

Daria Julkowska:
Yes, social media are clearly helpful in building networks. In the funding pathway of a research project, going from the basic to more translational aspects, to the clinical trial. Sometimes you need a small push with a relatively small envelope of money that helps you de-risk some of the results that you obtain. In Europe, this is where the biggest funding gaps actually exist, because we can find funding for basic and even translational research. When you go to the industry and collaborate with the industry, you are obviously much further. However, de-risking of some of the results of your research project is often neglected. It is very difficult to find sponsors to finance this part of the research. I think crowdfunding can be helpful here because we are talking sometimes about a small amount of money, perhaps 100,000 euros or dollars, that can be very helpful to move to the next step, but which is not sufficiently present in the funding chain.

"However, de-risking of some of the results of your research project is often neglected. It is very difficult to find sponsors to finance this part of the research. I think crowdfunding can be helpful here."

Julie Saba:
I was a part of another initiative. I was very fortunate to be a participant in one of the Ultragenyx bootcamps. Ultragenyx is an ultra-rare disease company that was founded by Emil Kakkis, one of the leaders in rare disease therapeutics. Out of the goodness of his heart, he, or individuals in his organization, established a bootcamp for parent-led organizations, advocacy groups. Twice a year, they hold a bootcamp and 35-40 organizations show up, usually just one or two people from each organization, and learn how to pitch, how to advocate for themselves, to express exactly what it is that they need, and then send it out into the universe or to pitch in front of someone and write directly in front of them in a conference room. I think that was a very nice educational experience that I was privileged to participate in.

"Twice a year, they hold a bootcamp and 35-40 organizations show up, usually just one or two people from each organization, and learn how to pitch, how to advocate for themselves, to express exactly what it is that they need, and then send it out into the universe or to pitch in front of someone and write directly in front of them in a conference room."

Erica Berg (*host*):
Fantastic. How could someone working in your space, or a researcher, find opportunities to learn, grow, partner and network? Are you just having conversations with people at meetings and learning about these opportunities? How can people learn about the opportunities that exist for growing in this space?

Julie Saba:
I wish it were well organized and there was a cheat sheet that you could just go to to figure out all the places for funding, advocacy, etc. It isn't like that. The last five years of my development as a rare disease researcher have been kind of hit and miss. It is the

same as in science. The more you network, the more meetings you attend, the more observations you make, the more people you meet. By and large, everyone that I have met has been so gracious in terms of sharing contacts, sharing opportunities, grant funding. Just participating in this event today, I have been making notes of my follow-up calls to each of you to try to learn more about the FDA and their listening sessions for advocacy groups and the kind of things that would be helpful for us in the future. I submitted an NIH grant for a natural history study in this disease, which would be an international study. But if it doesn't get funded, I am going to look up the FDA application. So, I wish it were a little bit more organized. But in the case of my disease, it was not, and it was a difficult road.

"I wish it were well organized and there was a cheat sheet that you could just go to to figure out all the places for funding, advocacy, etc."

Erica Berg (*host*):
Anyone else have a cheat sheet that we coud post?

Daria Julkowska:
No. What I can say is that the European Joint Programme on the Rare Diseases is trying to be a single entry point to the rare diseases community, or ecosystem, at least mostly for the European community, but also going beyond Europe. Today we are already encompassing 85% of the rare disease research community in Europe. We have this expertise at hand and can use a single help desk, not only through the information that we are providing on our website, of course, but also the funding opportunities, the services that we are providing, the expertise... So, anybody can come in with a specific request, and we, in a way, shorten the pathway to get to what they are looking for, either by being able to respond immediately by ourselves, or by mobilizing the network of experts that we have the possibility to connect with.

"European Joint Programme on the Rare Diseases is trying to be a single entry point to the rare diseases community, or ecosystem, at least mostly for the European community."

I am not knowledgeable about everything that is happening around the world or in the United States. When thinking about establishing a single portal that would put all the funding opportunities for rare diseases in one place, the reality is that it is very difficult because often rare diseases are not necessarily excluded as a topic, which means that calls for projects or funding opportunities that are addressed to larger topics that can also encompass rare diseases. So, this is very complicated.

Another thing that we are trying to work on, which is a very common request that we are getting not only from the researchers, but also from patient organizations, is how do I find my future collaborators or the people with whom I would like to build the project? The reality is, and I don't think that it is specific to Europe, you cannot impose on people to make themselves somehow visible. For example, you may have this kind of B2B or matchmaking tools that are implemented and are accompanying the open funding opportunities, but usually, the people who have already built their networks collaborate with their colleagues and are not necessarily open to look for some other collaborators. So those who are from the outside, they cannot see them. We are thinking about how we can build this kind of tool where the researchers working on different rare diseases or specific topics would be visible. This is something that can now be done with text mining, open science, artificial intelligence, and all those open data information. In the end, we hope that this is something that may be implementable in the near future.

"You may have this kind of B2B or matchmaking tools that are implemented and are accompanying the open funding opportunities, but usually, the people who have already built their networks collaborate with their colleagues and are not necessarily open to look for some other collaborators. So those who are from the outside, they cannot see them."

Ford Runge:
I just might add that in Economics, network externalities are actually a thing. We have criteria that can help us to understand how to facilitate networks that work better than others, so that it is possible to improve the efficiency with which communication in these networks occurs. Artificial intelligence is increasing, I think, the power of that capacity as we speak. So, I think that the application of some of those methods to the subset of networks that relate to rare diseases could be very beneficial.

Julie Saba:
I have had conversations with leaders in the National Office of Rare Disease and they have their finger on the pulse of what is going on throughout the NIH. Those conversations have also been helpful in directing me to funding opportunities and connecting me with people who have gone down the path before me. I think that is also a very useful starting point.

Erica Berg (*host*):
Is there a best point of entry to the FDA Orphan Drug opportunities, Christine?

Christine Meuller:
Yes, contacting myself is probably useful. I and several other project officers and our program director, Kathy Edelman, receive inquiries all the time about our program and whether folks may be a good fit for the funding opportunities that we have. We also know folks at our sister agencies and the NIH Office of Rare Disease Research, as well as the individual institutes based on the diseases maybe that somebody's asking us about on a regular

basis… the DOD funding opportunities as well. We are able to support each other in funding oftentimes as well. We sometimes have grants that have funding from different agencies for similar trials or for a natural history study with us, and then a clinical trial later with another agency. So, I think that is a good way. Julie mentioned not just the funding opportunities, but patient listening sessions that are held by our patient affairs staff for folks as they move along into clinical trials and may either be having issues or want to move a product forward and want the FDA to hear about what they think is a benefit or a risk, a good benefit risk ratio in terms of a possible treatment. Those are opportunities that folks can always get in touch with me about if they are interested as well.

Erica Berg (*host*):
I have a feeling you are about to get a lot of emails.

Julie Saba:
I just want to thank the FDA for all of the financial incentives such as the priority review voucher and things that have made a huge difference in terms of incentivizing the development of drugs for rare diseases. It may not quite fit into this topic, but it is very, very important. And it will hopefully be renewed.

Erica Berg (*host*):
Thank you once again to our panel and to Fondation Ipsen for enabling this conversation through their kind sponsorship. Goodbye everyone.

Advocacy in rare disease: Working the Regulatory Angle

Across the globe, regulatory landscapes are notoriously complex and difficult to navigate, yet laws regarding human health can literally be a matter of life and death. Diagnosis and treatment remain challenging for the more than 7,000 rare diseases impacting 350 million people worldwide. Policy makers set research funding agendas and make laws, such as the Orphan Drug Act, that can tip the balance on whether drug makers will pursue treatments for rare disease and make them accessible. Advocates play a critical role, getting the attention of lawmakers and making the case that regulations shape healthcare outcomes for people with rare disease.

In this webinar, policy experts, advocates, and political insiders will discuss:

- How to unravel the complexities of regulatory processes surrounding rare disease
- Strategies for getting access to lawmakers and what to say to make an impact
- Success stories about advocates who influenced policy, research funding, and access to treatments.

Panelists

Simone Boselli
Eurodis, Brussels, Belgium

Karin Hoelzer, D.V.M., Ph.D.
National Organization for Rare Disorders, Washington, DC

Julia Jenkins
EveryLifeFoundation, Washington, DC

Stuart Portman, M.P.H.
U.S. Senate Committee on Finance, Washington, DC

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

The Conversation

Erica Berg (*host*):
Hello everyone, and welcome to the fourth webinar in our 2023 Science series on advocacy in rare disease entitled "Working the Regulatory Angle". I am Erika Berg, Director and Senior Editor for Custom Publishing at Science, and I will be the moderator for this discussion. This is our third year exploring the challenges and successes in the rare diseases field. In previous years, our panelists have discussed diagnosis and detection, testing, research hurdles and opportunities, and mental health challenges. This year we have shifted our focus to advocacy. We have learned from advocacy experts from inside and outside the rare disease space covering such topics as crafting a compelling public narrative and securing funding. Today we will be having a conversation about how advocates can influence regulation. Across the globe, regulatory landscapes are notoriously complex and difficult to navigate. Yet laws regarding human health can literally be a matter of life and death.

Diagnosis and treatment remain challenging for the more than 7000 rare diseases impacting 350 million people worldwide. Policy makers set research funding agendas and make laws that can tip the balance on whether drug makers will pursue treatments for rare disease and make them accessible. Advocates play a critical role in getting the attention of lawmakers and making the case that regulations shape healthcare outcomes for people with rare disease. I would now like to take the opportunity to welcome a star-studded panel today. I will give each of them a chance to say hello and to introduce themselves.

Karin Hoelzer:
Hello, everyone. I am Karin Hoelzer and by training I am an infectious disease epidemiologist and a veterinarian. Earlier in my career, I spent a fair amount of time at the US Food and Drug Administration (FDA) and then in various health policy roles in Washington DC. Currently, I serve as the Director of Policy and Regulatory Affairs for the National Organization for Rare Disorders (NORD), where my job is to make sure that we elevate the patient's voice in government at every level. I am very excited to be here today.

Julia Jenkins:
My name is Julia Jenkins. I am the Executive Director at the EveryLife Foundation for Rare Diseases. My background is in grassroots organizing and government relations. At the EveryLife Foundation, we are a policy and advocacy organization. Much of what

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we do is helping patients navigate the regulatory challenges, both through the FDA and through the access environment.

Simone Boselli:
My name is Simone Boselli. I am the Public Affairs Director at EURORDIS-Rare Diseases Europe, which is the largest umbrella organization of patient organizations working to promote the rights of people living with rare diseases with the aspiration of improving their lives across borders. We are an organization working in over 70 countries with over 2500 members spanning across the globe. My role here is to work in advocacy and policy building, specifically with the European institutions and focusing primarily on research, development, authorization and accessibility of therapies for people living with rare diseases.

Stuart Portman:
My name is Stuart Portman. I serve as Senior Health Policy Advisor on the Senate Finance Committee for ranking member Mike Crapo. Previously, I worked on the Senate Finance Committee for Senator Chuck Grassley, and before that for Senator Orrin Hatch, who I had the pleasure of serving as his health advisor on all issues related to the FDA and rare diseases. Since 2017, I have handled all issues related to Medicaid and the Children's Health Insurance Program, which has provided a window into many of the payer discussions as it relates to rare diseases.

Erica Berg (*host*):
Thank you. I am going to put my first question to Karin. What are the rare disease issues that are impacted by regulation?

Karin Hoelzer:
In a nutshell, regulation impacts pretty much everything that we do in the rare disease space. The National Organization for Rare Disorders (NORD) was actually founded 40 years ago because a rare disease mom would not take no for an answer. The drug company that was making the drug that helped her son navigate his Tourette syndrome stopped making the drug because it was not economically feasible. As she was trying to find a way to change that, she started to realize that this was true for too many patients and families. The rare disease community came together and worked with Congress to pass a law to really change that and create more incentives to bring orphan drugs to market. We still have a huge unmet need, but we have been quite successful. Today, about half of all FDA-approved drugs are for orphan diseases. Now that we have more orphan products available, we see that coverage and reimbursement are becoming a bigger issue. We probably spend about half of our time advocating for appropriate access to these therapies. We have also started to realize that many of our patient groups want to be engaged in research but there are numerous regulations related to research funding and the conduct of research. So we work, for instance, through an FDA-funded research grant with the Critical Path Institute to help our community navigate this regulatory landscape and really bring the patient voice and the patient experience into research and to help create data. Ultimately, we hope to bring therapies to the more than 7000 rare diseases, many of whom currently do not have any treatments.

"Today, about half of all FDA-approved drugs are for orphan diseases. Now that we have more orphan products available, we see that coverage and reimbursement are becoming a bigger issue."

Erica Berg (*host*):
Julia, what are some of the unique challenges that advocates face when working with regulatory agencies in the context of rare diseases?

Julia Jenkins:
One of the biggest challenges for rare disease patients is that everything falls in the backpack of patients. NORD was founded by a parent advocate. Every drug that has been developed and approved in the rare disease space is likely due to a patient or their family doing the work in the very beginning; by de-risking it, finding the scientists and funding the scientists. When you get diagnosed with cancer, there are a ton of cancer organizations that can support you. Whereas in the rare disease space, if you are lucky enough to get your rare disease diagnosis, it usually falls on the individual patient to find their community, to start their own organization and to fund their research. That translates into these really small organizations that have to fundraise and navigate these really complex regulatory pathways and work with companies to bring patients to the trial and to design trials. A lot of this falls on the patients to become experts in their diseases and they have done so. Our patient community is amazing. To address the question of how they navigate the regulatory process, I think the FDA has really done an amazing job at working to improve patient engagement and patient-focused drug development at the FDA. On the access side, I think we are still in the beginning steps of that. When we started the foundation 15 years ago, we were not really working on access issues because there were not a lot of treatments to get access to. It has been a really exciting time to see so many drugs being developed for rare diseases that now these access barriers are becoming such an issue for our community, so it is going to take another big patient movement to help navigate the access environment. Back in 2012 it was the advocacy efforts around patient-focused drug development that became law in Prescription Drug User Fee Act (PDUFA) V, of the Food and Drug Administration Safety and Innovation Act (FDASIA) legislation, which I think Stuart worked on. That was really codifying in the statute that the patients could work on patient-focused drug development and requiring companies and the FDA to include them. We are probably going to need something like that in the future to help navigate the access environment.

"When you get diagnosed with cancer, there are a ton of cancer organizations that can support you. Whereas in the rare disease space, if you are lucky enough to get your rare disease diagnosis, it usually falls on the individual patient to find their community, to start their own organization and to fund their research."

Karin Hoelzer:
I think one other challenge that Julia has already alluded to, is that regulatory issues are complex and they take a long time. So one of the things that we at NORD have really prioritized from the beginning is to provide the education and training and the background that patients need to navigate the regulatory process. We currently have, for instance, an FDA grant to develop advanced educational materials related to FDA regulatory issues for patients so that patients can be better informed and can more easily participate in the complex regulatory process. Bringing a drug to market is a very complex issue that takes many years and many stakeholders, and it is usually very difficult for patients who are new to this space to understand how to effectively engage and be part of this process. So we are trying our best to help.

Erica Berg (*host*):
Stuart, maybe you could shed a little light on how rare disease issues are regulated in the United States? There are federal regulations and there are state regulations and I can imagine they span across everything from diagnosis to treatment. So maybe you could give us a little insight about how this happens.

Stuart Portman:
I will focus more on the FDA and the Centers for Medicare and Medicaid services (CMS) side of this. Obviously, there are the mixed emotions of having the ability to receive a diagnosis where you are excited that you have something that you can work forward from. The National Institutes of Health (NIH) play a role in this aspect as do a lot of other funders of research in regards to the points that were previously made. When talking about the federal role in the US, the conversations usually start when it comes to the FDA and the different approaches to how we treat orphan products. Whether we are talking about small molecule drugs, cell therapies, gene therapies or, in some cases, generic treatments that work for certain additional indications or for certain symptoms, the regulatory frameworks are different. Even within FDA, if you are going through the Center for Drug Evaluation and Research (CDER), on the drug side, or, the Center for Biologics Evaluation and Research (CBER), on the biologic side, it is important that the expertise is aligned within the agency and to make sure that there is a shared vision. Those regulatory actions take place within the FDA, however a lot of the direction can also come from the Department of Health and Human Services and from the White House. In the rare disease space, we have seen successes occasionally when there is that broader leadership as it relates to these issues. I think it is also important to note that when speaking about the regulatory differences at the FDA, there are traditional approvals and there are times when accelerated approval will be granted. I think that you also create additional incentives for innovators in this space with priority review vouchers, for some of the rare diseases for children or some of the pediatric review vouchers, just some of the ways to make sure that the incentives exist to enter this space when there are so many competing interests.

One must also make sure that the FDA has what they need in order to make the right judgment call. There has been a lot that has gone through, and you do not want situations where rare disease products only make it through because of leadership. You want the reviewers to also have the expertise to make these decisions that are informed by science and data so that they are based on safety and efficacy. I would also say that when you shift from the FDA side to the Centers for Medicare and Medicaid services (CMS), which would be the largest payer as the combination of Medicare, Medicaid, and the Children's Health Insurance Program, as well as marketplace coverage, those discussions, primarily Medicare and Medicaid, guide a lot of discussions. Too frequently in the rare disease space, the focus has been on the FDA because of the journey and the odyssey to get there, and we have lost the ability to bring along some of our coverage experts into the mix. That has led to these delays where there is a lack of understanding. Where you have people that are confusing accelerated approval in the United States and conditional approval from Europe, which are different things, but they are frequently conflated. For those of us in the space, it is always very frustrating because you want to make sure that when you are talking about coverage, you are talking about is there a guarantee of coverage and can there be a rebate? Is it federally authorized? Is it state-based? Is it something supplemental that is determined by the manufacturer to work with a state or a payer of some kind? What kind of utilization management controls are going to be there? Some of these can be federal and some of them can be state. Are we talking about prior authorizations? The use of step therapies? Sometimes there is an additional fail first policy that could be included. Those all play a role in access to a treatment and the regulations that flow from CMS oftentimes could use a little more connectivity to the decisions and approvals that come out of the FDA. I think that we see a lot of growing interest with, as Julia mentioned, patient-focused drug development. It is still novel to talk about surrogate endpoints for those that are on the payer side, while for those on the FDA side, this is a very well discussed area. The people understand, especially when talking about rare diseases, that your clinical trial design is inherently different. That is not always understood by those that live their lives solely in the coverage realm and understanding how you can have an endpoint that is not solely clinical in nature is something that stands out. Additional education could be helpful there. So there is a lot in the federal space within the United States, but there are also some state-based decisions on the public health side, particularly around newborn screening and a lot of the decisions that take place related to public health.

"Too frequently in the rare disease space, the focus has been on the FDA because of the journey and the odyssey to get there, and we have lost the ability to bring along some of our coverage experts into the mix. That has led to these delays where there is a lack of understanding."

When you are speaking about coverage, Medicaid is the largest payer in this space, currently serving about 92 million people, which is a very large population. Prior to the pandemic, it was closer to about 74 million or so, which is still a very large population and the largest payer for rare diseases. So when we have

these discussions and need to figure out how a program that is operated state by state plays a role, it creates both opportunities for rare disease advocacy at the state level to enhance what has happened federally, but there are challenges with making sure that there is access to treatments and that no unnecessary utilization controls are put forward because of unrelated access concerns that deal with price. When speaking to the nature of how these coverage discussions play out, including the role of pharmacy and therapeutics committees within a state and the use of additional managed care entities to make some decisions versus the state making all decisions, things get very complex very quickly. There should be the shared vision and goal of making sure that patients with rare diseases have access to the treatments that can actually help them improve their lives and, with the emergence of the science that we are seeing today, in some cases, potentially cure them.

"There should be the shared vision and goal of making sure that patients with rare diseases have access to the treatments that can actually help them improve their lives and, with the emergence of the science that we are seeing today, in some cases, potentially cure them."

Erica Berg (*host*):

Maybe we can clear up some of the European Medicine Agency (EMA) and FDA confusion happening. Simone, what can you tell us about how things are done in Europe and elsewhere?

Simone Boselli:

I will focus on Europe, which is where I know best, along with the UK. I recognize a lot of the issues that Stuart has just outlined in the European context, which are probably aggravated by the dichotomy between the regulatory approvals that, particularly for innovative therapies, are centralized at the European level with the European Medicine Agency. The EMA was created in 1995 to harmonize the work of the existing national medicine regulatory bodies, particularly for the quality, efficacy and safety of the medicine that came into the European market. This is an issue that dates almost as far back as the birth of the European project itself in 1965, when the first common decision on the approximation of national laws regarding medicine came about following the thalidomide crisis.

Since 1995, the European agencies remit has expanded, and the agency has been responsible for products related to the specialized area of rare diseases. I think here a parenthesis should be made as EURORDIS was effectively created to bring to Europe that efficient environment of incentives created in the US. And if anything, we succeeded in the first step to create a much broader set of policies on rare diseases that stem through that landmark legislation of 2000 and also for medicine specifically for children through the pediatric regulation of 2006, and a regulation on advanced therapy medicine, often called Advanced Therapy Medicinal Products (ATMPs), since 2007. Another characteristic of the 2000 orphan medicinal product regulation is that it opened up the official involvement of patients and their representatives as well as healthcare professionals at the EMA. It is in this structure made up of committees that patients can represent their voice both through the appointed members, of which EURORDIS has a few in both the Committee for Orphan Medicinal Products (COMP) and the Committee for Advanced Therapies (CAT), as well as in the scientific advice group that supports the work of the agency towards authorization at the European level. We have an agency that represents and authorizes therapies, but things get a little bit more complicated when it comes to the access part, as there is a product that for rare diseases is solely decided at a central level, that goes to an access system that is fragmented in at least 27 different markets because of the fundamental idiosyncrasy of the European project in health. The products are regulated at the European level. The public health systems are regulated at national and also the regional and hospital levels. Therefore, all of the issues that Stuart and the other panelists mentioned in relation to access are exacerbated by these differences at the country level. To the point that in some countries therapies are not even reaching the patients. In some countries there are delays of 3 to 4 years, while in others, namely Germany and to some extent Italy and France, things are much better. From the perspective of an umbrella organization, this inequity is not sustainable, particularly as the science that we are seeing at the moment is phenomenal and potentially represents a hope for a cure that only a few years back we could not have dreamed of.

Erica Berg (*host*):

As a follow up question, Simone, are there any current laws that are being debated that would impact rare diseases? What is going on right now that we should be aware of?

Simone Boselli:

A lot! It is exciting and yet challenging at the same time. The European Commission has embarked in a proposed reform of the entire pharmaceutical legislation framework, which included the general pharmaceutical legislation, as well as the specific regulations for orphan medicinal products and therapies for children. These regulations have been very successful but there is a recognition that some issues need to be addressed if Europe wants to stay competitive and provide access to innovative therapies to the largest possible number of people in Europe. These are not only questions related to affordability but are also questions related to the speed of regulatory approval, which is currently still a little bit behind when compared to the US.

There is recognition that some of the incentives that have been provided to the industry have not yielded the outcomes that we have expected and therefore a recalibration might be needed. On the other hand, talks of such sweeping changes, which include for the first time an emphasis on access issues, have already frightened a lot of people, particularly in the R&D based industry and, to be honest, us as well, because we need a thriving European ecosystem that is not solely based on the research that comes out of the US. Furthermore, at a national level, we have a number of countries that are looking once again at introducing or improving their existing frame-

works of national plans for rare diseases. Sweden, for example, has announced that they will be starting work on their first national plan in October. France, on the other hand, is already on their fourth national plan. We at EURORDIS need to continue to advocate for a comprehensive view and therefore a European action plan that brings together all of these parts.

Erica Berg (*host*):
Thank you. Stuart, what is going on in the US?

Stuart Portman:
There are always many different bills in Congress and regulatory actions that are under consideration. I know others can speak to this as well, but I would say that there are many things that stand out right now where there is a growing interest. Medicaid payment policy is rather complex but allowing payment for value and whether that means the ability to have a non-payment or a reduced payment or a payment over time and a sort of mortgage model, those conversations, while there is a lot of support for any sort of outcome-based arrangement, require legislative changes to be as effective as they could be. There are conversations that have been going on for a while, but that have become recently vocally bipartisan. There is a potential for change to happen there, just to open up access. I am not one who thinks it is going to happen tomorrow, but I think it could happen in the near future as a way to make sure that the largest payer for individuals with rare diseases actually can cover those products, especially with the increasing innovation and novelty of the treatments that are coming down the pipeline right now.

We want to make sure that the system is able to handle those products and the potential cost implications of those products. You have budget operators that are alarmed, even though they are excited, and it is important that any legislative regulatory approaches can try to manage all of those different interests. There are also conversations related to how do we ensure access to centers of excellence for treatment across state lines. While obviously it is a different conversation, making sure that providers with expertise in some states are able to treat individuals more seamlessly is important. A lot of the work of NORD and EveryLife, goes into helping make sure that patients can actually get to the treatment and legislatively there are efforts to try to make that easier and less burdensome.

There is also a lot of focus on implementation of the recent changes to the Medicare program. I do not want to go too far into the weeds, but there were potential areas that could have unintended consequences. I am sure there is going to be a focus on whether or not those unintended consequences bear out because anything that reduces innovation in this space is detrimental to patient access and their future care. Similarly there is regulatory work going on that, especially in the Medicaid program, could create some sort of disincentives for investment in this space because of rebate obligations that would be put onto manufacturers. So those are just a few things that folks are keeping an eye on here while also working on some of these other legislative efforts.

Julia Jenkins:
Can I just paint a picture for the audience too? When we talk about global perspective and why what is happening in Europe and in the US and globally is really important, it is because when we talk about a rare disease, and especially an ultra rare disease, a company is needing to ensure access to as many of those rare disease patients as possible for them to get investors to invest in their drug. If access is being blocked in some of the European countries or some of the US states or is not going to be reimbursed, they will not develop the drug. We would therefore love to see a more global action happening. To think about rare diseases and only being able to treat the patients in Europe and the US also really limits the scope. We know there are so many other rare disease families out there in the world that are not even going to have an opportunity to access treatment in their lifetime. If we really want to be successful, we have to look at a global model for these drug companies to really try to invest in these ultra rare diseases. That is why it matters whether or not the US pay organizations care about what is happening in Europe. We have to, as it is a global drug development ecosystem. So to have that perspective is really important as we move through the different countries and as they navigate the regulations, we also need to be looking at what is happening elsewhere.

"We know there are so many other rare disease families out there in the world that are not even going to have an opportunity to access treatment in their lifetime. If we really want to be successful, we have to look at a global model for these drug companies to really try to invest in these ultra rare diseases."

Karin Hoelzer:
To maybe briefly dovetail with what Julia said there has been a growing recognition even in the US that there are large parts of the patient population that have a much harder time to participate in clinical trials and to benefit from the treatments. So there has really been a lot of emphasis both on the regulatory side and on the congressional side to improve access to these life-saving therapies. That may include, for instance, telehealth, as Stuart mentioned, and bringing trials into the patient's home. Many of our rare disease patients have a hard time traveling, but we know that many of them have to travel 60 miles or more to seek care and oftentimes fly across state lines to participate in clinical trials, which puts a tremendous burden on our patients and our families. Leveraging the learnings from the COVID pandemic and new technologies to really break down these barriers to encourage equitable access and participation in research so that patients can benefit from these therapies is tremendously important for our community. We see a lot of proposals and a lot of emphasis luckily in that area at the federal and state level.

Erica Berg (*host*):
So we have heard a lot of complexity and challenges. Let us turn our attention to the patient advocate. Julia, with all of these complexities, how can advocates stay informed about regulations and where should they be placing their energy in

terms of advocacy efforts to get these changes that will help them?

Julia Jenkins:
I talked earlier about really small patient organizations and how this creates another burden on these tiny patient organizations. I think that is why it is so important that there are organizations like NORD and EURORDIS and EveryLife Foundation to help track all of those regulations. The National Health Council as well will do draft guidance comments. NORD and the EveryLife Foundation do comments. We have a community congress where we work with hundreds of patient organizations and industry partners to inform our comments so that there is collaboration between the different stakeholders. Because it is a lot of work to track the regulations and to provide comments and feedbacks in the hopes of getting regulators to really understand the patient experience and perspective. It is not always successful. In that case you have to take action and go back to the hill and lobby Stuart, who is an amazing rare disease advocate in his role, to really get other members of Congress to understand how the drug development system is impacted by legislation.

People in Congress and people at home do not realize that it is laws and regulations that are impacting their ability to get a therapy. Once that light bulb turns on and they realize that they need to be a policy advocate, it is a really exciting transformation and it gives the individual patient that power to be able to have a voice and to contact their member of Congress and advocate for needed changes. We host Rare Disease Week on Capitol Hill, which brings nearly a thousand advocates together to fly in and meet with their members in person. We were happy to partner with EURORDIS earlier this year to help bring patients to Parliament for the very first time. So it is really a great opportunity to make sure that patients have the chance to be heard by their policy makers.

"People in Congress and people at home do not realize that it is laws and regulations that are impacting their ability to get a therapy. Once that light bulb turns on and they realize that they need to be a policy advocate, it is a really exciting transformation and it gives the individual patient that power to be able to have a voice and to contact their member of Congress and advocate for needed changes."

Erica Berg (*host*):
Thank you. Anything to add for Europe as far as ways that patient advocates can stay informed of regulatory changes and things that are happening right now that they should make a statement about?

Simone Boselli:
Well, we definitely do try to maintain a regular conversation with all of our members. We primarily work with national alliances because you have to remember that we do not all speak the same language and therefore there are issues related to that specifically, although many make the efforts to do so. That is why we brought over 40 different rare disease advocates of 10 to 15 different nationalities to Brussels, because the geographical providence is also very important here and the language is as well. The main way that we are trying to do it is through our empowerment programs such as the EURORDIS Open Academy, and particularly what we used to call summer school, which has dealt with the topic of regulatory development. Since 2009/2010, in cooperation with the European Medicine Agency, we have trained over 500 patient experts that, in some cases, have continued their own education. Those that have continued have become members of committees at the European Medicines Agency (EMA) and they are now advocating for regulatory changes in their own disease area or in other disease areas, in the agency but also at a national level. So that is what we are trying to do, in addition to communication, plus the work that we do around Rare Disease Day and on an individual basis.

Erica Berg (*host*):
Stuart, so how can an advocate reach out to their elected representative? They could go through one of these organizations and work through there, but can patient advocates reach out directly and what are some best practices?

Stuart Portman:
Of course going through an organization is always helpful, but it is not necessary in the sense that there are many members that will take meetings or have their staff take meetings. Especially today, there are opportunities as a rare disease advocate to educate, which feels like such a innate part of any rare disease advocate as they are used to doing it all the time, but there are a lot of staff that help advise their bosses (the members) that all could use a refresher in understanding what it means to live with a rare disease. Understanding the various types of care and providers that are needed and all the different appointments. The impact on day-to-day life. The fact that a current treatment regimen may not be some oral therapy. It might involve infusions, it might involve hospital stays or it might involve additional use of durable medical equipment. Understanding what that looks like is something that is very hard to put into a letter or an email, even if it is heartfelt. It is best shared when it can be verbalized and ideally verbalized in person because it opens up a lot of doors to making sure that someone has empathy and understanding and can really start to see that this is not something that you can just wave a magic wand and legislatively everyone will agree to solve it. There is complexity here and you want to make sure that you help as many people as possible. Advocates that ask for meetings tend to get those meetings. Most offices are not looking to turn away a rare disease patient from being able to express what their lived experience is and how they envision a difference in the future. I would say organizations tend to be better equipped to talk about how to fix something through regulation or legislation, but to understand the human voice that goes behind a lot of those pieces, individuals have the ability to ask for those meetings and it is really as simple as writing in to ask for a meeting or calling or organiz-

ing through an association or organization. I know of very few instances that someone ever said no, when someone wanted to share that experience with them. One thing to keep in mind is that a lot of times people want to talk to the member, and frequently that happens, but sometimes they feel let down if they end up talking to the staff. I am not just saying that as a staff member. I would say that there are actual benefits to educating the staff because frequently they are in the room developing the legislative text based on a broader directive from the member of Congress and then they go back with that approach to the member of Congress for approval. Sometimes members are deeply involved and sometimes they are less involved, and they hand off a lot of the responsibility to their staff. So never look at a staff-based conversation as a negative because you never know where someone is going to be five or ten years down the road and could be of assistance. Building allies on this journey is a goal across the board.

Karin Hoelzer:
There are a variety of different ways for advocates to have their voice heard. Obviously meetings with Congress and providing testimony are great opportunities to tell your story. But I know that for many patients this may be overwhelming at first or it may not be physically feasible. So they have a variety of other ways, such as writing letters. We regularly help our community to write letters to their Congressmen on legislation. You can also tell your story through social media or through blogs or provide comments on dockets. There are a variety of different ways that are more or less involved and more or less time consuming. I really want to make sure that everybody feels that there is a path for you to have your story heard regardless of what is feasible or what is comfortable in your life. It does not have to be a meeting with congress, even though that is a great opportunity.

Erica Berg (*host*):
Karin, could you share a success story where advocacy efforts led to a positive regulatory outcome?

Karin Hoelzer:
Absolutely! Julia already mentioned the history of patient-focused drug development starting with the 2012 User Fee Act, where the FDA committed to bringing the patient voice as an integral part of the drug development process. It is really important to make sure that what is measured in a clinical trial actually matters to patients. That the risks and benefits that a patient has to consider and whether a patient wants to take a drug is appropriately captured in the drug development process. This was really revolutionary and required a lot of engagement from the patient community to make this happen. Then there was working with Congress to make patient-focused drug development a more integral part and a more standard part of the drug development process. We have come a tremendous way. We have seen the FDA not only hold a lot of patient-focused drug development meetings, but also develop tools and provide guidance for the community for how to bring the patient voice more effectively into these meetings. We have seen the creation of patient listening sessions, which are somewhat smaller, more intimate and in some instances a different way for patients to share their story with the FDA reviewers who will be reviewing the application. So, we have seen a tremendous trajectory over the last 10 or more years in bringing the patient voice and the patient experience into the drug development process. On the coverage and reimbursement side, we, at NORD and others, have worked very closely with the Centers for Medicaid and Medicare (CMS) to make sure that patient experience data is incorporated. For the first time this fall, the price of some prescription drugs will be negotiated to really capture what the value of these therapies is in particular for rare disease patients. We have really seen CMS embrace that idea and just earlier this summer, CMS committed to holding patient listening sessions to really find a way to bring that vital patient voice into the negotiation process. I think that is a really great example of how continuous interaction with a regulator really brings value, but it also demonstrates how many years it takes to bring about that change.

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Julia Jenkins:
Just to highlight too, that this legislation impacts all diseases but it was led by the rare disease community. The work we do in the rare disease space really helps all patients everywhere. I know you said seven thousand, but I think the number of rare diseases is now estimated to be closer to 10,000 different rare diseases. Therefore, the work that we are doing in drug development and regulations is really impacting the entire world with getting access to innovative therapies.

Erica Berg (*host*):
That is fantastic. One thing we have been trying to do this year is to get insights from outside the rare disease space, in order to understand what advocacy strategies work. Stuart, I was wondering if you have an example of a successful advocacy strategy that worked for the passage of legislation in Congress that we could learn from?

Stuart Portman:
I have been fortunate enough to see the passage of a lot of legislation and there are big ticket items that draw a lot of attention and then there are smaller pieces as well, where it is about how you build that coalition of support. I think the passage of 10 years of the Children's Health Insurance program is a good example of how a coalition came together. For the non-US based audience, the Children's Health Insurance program operates at an income threshold that is above where Medicaid is for children and some eligible adults. It is an additional way to provide coverage and while it is quite comprehensive, it is also authorized in a time-limited way as a block grant. The Children's Health Insurance program was up for reauthorization in 2017. So at the end of 2017, going into 2018, there were debates on how long it could go, and there was a desire led by my boss at the time, Senator Orrin Hatch (due to the fact that he helped create the program in 1997), to have it go for another 10 years rather than a shorter period of time. That effort required advocates in the children's health space to come together from across the more traditional advocacy groups, involving the providers and the payers and everyone had to come. We had weekly sessions where they all came together into one room and everyone could voice what was working and what was not working. We could voice areas where we thought additional reforms might be needed and people could push back. There was a weekly conversation at the committee level while those organizations had additional conversations with members of Congress throughout the week. Then we would all come back and have those follow-up discussions and figure out where people agreed, and where people could be comfortable, as we worked towards this broader strategy of how do you get to 10 years. The senator helped convince other members that it was better to go longer term, for those that were on the fence, as opposed to coming to do a check-in on the program later. The advocates bought into the fact that continuity of care in this program would be really amazing for a decade. So they could have these committee-based conversations that were happening with both parties, not usually together, but sometimes together. Just so that everyone knew that we were all working towards the same goal while still having those discussions at a more state-based level as well. It was a way to bring experts at the state government and experts in the advocacy space together with federal policy makers and it really was a successful effort as we managed to get 10 years of the Children's Health Insurance Program.

Erica Berg (*host*):
We have talked a lot about how important it is to have a global perspective for getting anything done in the rare disease space. Simone, I was wondering if you could talk about any successful examples of cross-border advocacy collaborations that have had a successful outcome?

Simone Boselli:
As part of the global work that Julia mentioned earlier, I think the work that has been done at United Nations with the resolution on people living with rare diseases just a couple of years ago, was a real pinnacle of global advocacy that required going beyond the geographical territories and bringing together a common platform to advocate for equal rights to access of healthcare across the world. Despite all of our challenges, we need to bear in mind that we are in a much more fortunate position than other people around the world. As Julia was saying earlier on, without a global mindset it is not possible to access potentially lifesaving or life transformative therapies, or even to ensure the basics of diagnosis and dignity of care, or to end discrimination and stigma. The best strategies are those that go across borders and cover all disease area while preserving the individual disease issues that are of clear importance to each patient. That is how we try to work in Europe as well, given that we have to bring a lot of people from different countries together.

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Erica Berg (*host*):
As an umbrella organization, how do you allocate resources when you are covering so many different diseases and how do you decide what regulatory issues you are going focus your efforts on?

Simone Boselli:
Fortunately, as the European Medicine Agency is currently structured with a specific committee for orphan medicinal products with committees for advanced therapy, we know where to focus our work. At EURORDIS, as I mentioned before, we have the Open Academy that trains our experts, who will then be requested by the European agency to provide insights into their daily life, what are the common patient experiences, what are the outcomes and the measurements that are needed to quantify how a treatment is safe and efficacious. We are also now entering 15 years of work in health technology assessment, which is separate from the authorization process. It will be harmonized as of 2025, but as Karin was saying earlier how do we present that when it comes to reimbursement decisions and how can people and organizations be heard? What we try to instill, which is not always easy to do, is that if we work for the overall sake of the rare disease community, the benefit to the individual diseases will come as well.

Karin Hoelzer:
It is actually quite similar for us. Going back to our roots, we were established by uniting the voice across rare diseases. It allowed for a more compelling voice and to bring the Orphan Drug Act to pass, and that is really still our guiding star. We try to focus on issues that are cross-cutting and where speaking across different rare disease communities can really help elevate the story. We have about 330 disease-specific member organizations and we work with hundreds more communities that are in the process of developing rare disease advocacy groups. We see a lot of our job, just like Stuart said, in elevating that voice, in helping to share best practices from one community to another, and, again, in uniting so that we as a rare disease community can have a louder voice and ultimately be more successful in overcoming the barriers for our patients.

Erica Berg (*host*):
And on that note, we will unfortunately have to stop there. Many thanks to all of our panelists for being here, it has been a delight talking with you all. Thank you once again to our panel and to Fondation Ipsen for enabling this conversation through their kind sponsorship.

Advocacy in rare disease: Taking care of caregivers

The Covid-19 pandemic brought into focus for many the enormous stress and sacrifice experienced by caregivers. Those caring for individuals with rare diseases have long faced challenges, from navigating complex medical systems to providing emotional support for their loved ones. Many caregivers also feel the need to act as advocates for their loved ones, working with governments, patient groups, and other stakeholders to try to improve the lives of those under their care. Too often, the plight of the caregiver themself is overlooked, but advocates are working to make change. In this panel discussion, we will explore advocacy efforts aimed at easing the burden of caregiving for rare diseases.

In this webinar, participants will learn about:

- The unique challenges caregivers of people with rare diseases face,
- Caregiver advocacy action from outside the rare disease space, and
- Success stories about advocacy efforts that are easing the burden of caregiving in rare diseases.

Panelists

Maria Della Rocca
Global Genes, Washington, DC

Catherine Alicia Georges
Lehman College, Bronx, New York

Parvathy Krishnan
Krishnan Family Foundation, Cary, North Carolina

Amy Jayne McKnight
Queen's University Belfast, Northern Ireland

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

The Conversation

Erica Gebel Berg (*host*):
Hello everyone and welcome to our fifth webinar in our 2023 science series on advocacy in rare disease, entitled Taking Care of Caregivers. *I am Erica Berg, Director and Senior Editor for Custom Publishing at Science, and I will be the moderator for this discussion.*

The COVID-19 pandemic brought into focus for many the enormous stress and sacrifice experienced by caregivers. Those caring for individuals with rare diseases have long faced challenges from navigating complex medical systems to providing emotional support for their loved ones. Many caregivers also feel the need to act as advocates for their loved ones, working with governments, patient groups and other stakeholders to try to improve the lives of those under their care. Too often, the plate of the caregivers themselves is overlooked, but advocates are working to make change.

In this panel discussion, we will explore the advocacy efforts aimed at easing the burden of caregiving for rare diseases. I would now like to take the opportunity to welcome a truly wonderful panel today.

Catherine Alicia Georges:
My name is Catherine Alicia Georges and I have been a caregiver myself, as my husband had Parkinson's for 14 years. I am also a registered nurse and even though I knew a whole lot, it was important for me to learn more about advocacy and caregiving. In my role on the board of AARP and being on the RAISE Family Caregiving Council, I have learned so much more from caregivers across this country so I am honored to be part of this panel.

Parvathy Krishnan:
My name is Parvathy Krishnan and I am a mom to two medically complex children with multiple genetic conditions. They receive care across various institutions in the country and so we travel far and wide to provide them with the care that they need. My daughter passed away when she was four years old after living with multiple medical conditions. Caregiving looks very different now as a mom to medically complex children than what it was when I was a registered dietician doing clinical care. Life took on a completely different meaning. Through my work and my experience in advocating for my children on a micro level, I then took it to a macro level by starting our own foundation and supporting caregivers and patients in our community.

Broadcast Date: 11 October 2023 Access this webinar here

Amy Jayne McKnight:
I am a professor of molecular epidemiology and public health at Queen's University Belfast. Effectively, I run really busy research laboratories and I have a passionate interest in supporting rare disease communities, whether that is improving diagnosis or helping people live as well as possible for as long as possible. I have been really fortunate to be able to participate in multiple working groups that have influenced rare disease policy and practice. I also co-lead the All Ireland Rare Disease Interdisciplinary Research Network, known as RAiN.

Maria Della Rocca:
My name is Maria Della Rocca. I am trained as a bilingual genetic counselor and have been in the rare disease space for over 20 years. I have served in multiple capacities in the clinical setting as well as on the support and education side. In addition to providing support and working very closely with lots of families that have rare and genetic diseases, I have also had the opportunity to work very closely with my family members, some of whom have been diagnosed with rare diseases. Seeing the caregiver's perspective and providing support to some of those caregivers is another perspective that I bring to the table today.

Erica Gebel Berg (*host*):
I am going to put the first question to Parvathy. Can you give us an overview of some of the unique challenges that caregivers of individuals with rare diseases face compared to caregivers of individuals with more common conditions?

Parvathy Krishnan:
I think I would like to start off by saying that although it sounds unique and exotic, it really is not. It is painful and very difficult to navigate. I think the most basic difference between a "normal", more prevalent condition versus a rare disease is that when you walk into your doctor's office and your loved one receives a diagnosis of diabetes, there is usually a plan. There is usually a multistep plan, outlining that we are going to try this and if this does not work, we are going to try something else. If they do not work then we have 10 other plans that we can try. With my son, when we were given the genetic diagnosis of a cancer predisposition syndrome, I said, "Okay, what is the plan? Tell me the plan." The doctor replied, "We do not really have a plan because we do not really know much about this condition." So I said, "Okay, where do I go to find the experts that know more about this condition?" They said, "There are not very many experts in our state or in our country. There is an international consortium out of Canada but they mainly do research in labs". I asked, "What does that mean? How are we going to care for our child?" Our very basic questions of what can we do to save our child was the biggest difference that I found. When my daughter was six months old and we were given a genetic diagnosis of Bardet-Biedl syndrome, which we had never heard of until then, we said, "Okay, now what?" They told us, "There is no cure for this condition. What we do know is that she is going to go blind at some point. She is going to be morbidly obese, developmentally delayed, and will have kidney failure at some point in her life. If we come to know of something else, we will tell you what to do." Right there, the playing field was changed. We did not know what to do with our child. We did not know how to care for our child. After doing more research in this space, I think it stems from the very understanding that people view parent caregivers as "this is what they would normally do". You have a child and you care for your child. I do not consider myself as just a caregiver. I consider myself a medical parent. Those are two very different things. As a caregiver, I would take my child to school and soccer practice and whatever clubs I had to go to, or if my child had the flu, I would take care of them. As a medical parent, not only am I her or his mom, but I am also a quasi-doctor, a therapist, an Uber driver, a pharmacist, and I am fulfilling so many more roles that are not included in what we would normally call caregiving. Therefore, I think that the biggest difference is the unavailability of treatments and the simplest one is that we take on many additional roles as a caregiver and it is chronic and lasts throughout their lifespan.

> ***"I do not consider myself as just a caregiver. I consider myself a medical parent. Those are two very different things."***

Erica Gebel Berg (*host*):
Thank you. My next question is for Maria. What are the most pressing needs and concerns expressed by caregivers in the rare disease community and how have these evolved over time?

Maria Della Rocca:
That is a great question. I think the impact and needs may vary from rare disease to rare disease. It depends on the specific disease, the severity, the prognosis, the prevalence, and the accessibility to resources, as well as the available support systems. The needs and concerns may also evolve from time to time as circumstances change. In fact, it is not uncommon to hear some caregivers say that caring for a person with a rare disease feels like riding a rollercoaster. There are highs and there are lows and then the pressing needs and concerns of the caregiver may also vary based on other factors, such as if these caregivers are from underrepresented or historically marginalized groups. They often mention that they do not feel supported because they encounter healthcare providers who cannot relate to or are not aware of their cultural or language differences.

You also have the male caregivers. As we all know, most resources that are available tend to focus primarily on female caregivers. This is typically because females are the ones that take on that role. You have the single parent caregivers who are solely responsible for taking on the care of their children, which leads to a greater financial and task burden for them. There are also, of course, the children who step in as caregivers to care for their parents who might be living with a rare disease. Approximately 3.4 million children in the US assist with the care of a family member. This number does not even account for children who are under 18 years of age. Younger children may also step in to help with the caregiving responsibilities of a parent or some other family member or sibling. It is important for us to remember

that they are children and we can enlist their assistance for age appropriate tasks, but not impede on their school or other free time activities. Finally, there is the caregiver who is also a patient. Sometimes, as we know, some of these rare diseases may be inherited and passed on from parent to child. So that is another group that has their own set of challenges that involve not only caring for themselves, but also for their children. So, the impact of the rare diseases on caregivers is seen in different facets of their lives. The time required to deal with the rare disease of their loved one takes away from spending it on interactions with others, such as with their other children, with their spouses, with other family members, or with friends.

Oftentimes, the time spent caring for others may interfere with the ability for caregivers to pursue their own activities and also practice self-care. I think Parvathy already mentioned that rare caregivers often have to wear a myriad of hats. They have to serve as experts, as the majority of people they encounter, including healthcare professionals, are unfamiliar with rare conditions. Additionally, some of these rare caregivers also take on the role of researcher, innovator, organizer, fundraiser, and even policy work. I work for Global Genes and as the Senior Director of Support and Education Programs there we see a lot of the inquiries that come in from caregivers into our RARE concierge program. They are looking for assistance in the area of financial resources, support resources, and connection to others living with the rare disease, as well as help finding experts and specialists. So, those are some of the top reasons why people contact us and caregivers are looking for support in those areas.

"In fact, it is not uncommon to hear some caregivers say that caring for a person with a rare disease feels like riding a rollercoaster."

Erica Gebel Berg (*host*):

Amy, this next question is for you. I was curious, what got you interested in research related to rare diseases and specifically caregiving?

Amy Jayne McKnight:

My family has multiple rare diseases. It is a world I have always been involved with outside of academia. I sat on my first rare disease charity committee when I was 16 years old and was always volunteering. My parents have complex medical needs, as do my husband and my daughter. My day job was about identifying biomarkers for disease, in other words helping people get a diagnosis and put a name to their disease. Gradually, I became able to build more and more of a rare disease emphasis into my research. There are more than 10 million caregivers across the UK. About 12% of the population of Northern Ireland contributes more than 2.4 million hours of unpaid work per week. And yet supporting caregivers is so neglected. There are so many challenges that I see as a caregiver for multiple members of my own family with rare diseases, and more formally as a rare disease researcher, that I guess I am passionate about trying to improve the support that is available to caregivers.

"There are more than 10 million caregivers across the UK. About 12% of the population of Northern Ireland contributes more than 2.4 million hours of unpaid work per week. And yet supporting caregivers is so neglected."

Erica Gebel Berg (*host*):

Alicia, you have heard a lot about caregiving in the rare disease space and you have a lot of experience thinking about caregiving for more common conditions. What do you think are the main differences between the advocacy issues that come from caregivers in the rare disease space versus caregivers for people with more common conditions such as those affecting older adults?

Catherine Alicia Georges:

I think Parvathy and Maria were very clear in articulating some of the differences. It is very true that when you have a child or a family member with a rare disease, there is very little that the main health providers really know or can tell you about the trajectory of the disease or how to really give you the kind of support you need in regard to treatment. Treatment may not even be available to mitigate the disease. As Parvathy said, there are no protocols as we have for diabetes and for high blood pressure. For someone who has had a stroke we can say "these are the things you need to do and this is what you should be doing." The other issue is that they are a younger group of people overall, even though people may live longer than had been expected 20 years ago when one was diagnosed with a rare disease. However, there is still a shorter life expectancy. That is the difference. The majority of caregivers are dealing with people who may be 50 plus, who therefore have a different life expectancy. We are talking about older adults living to be 100. There may also be some commonalities. The burden of the disease is still the same, whether one is caring for someone with dementia or someone who has had a stroke, or somebody with physical disabilities. The burden and the stress of caregiving remains the same. That is not different. Being a caregiver is a critical role that many of us have assumed. The problem is that we have not had the support. This is not to say that families are not trying hard, but we have not had the support that we need from healthcare professionals to be able to support us through this whole journey. So, I see some differences, such as age and life expectancy, but there are so many commonalities in this whole caregiving space in persons with rare diseases and in those who we know who may have dementia or other chronic illnesses.

"Being a caregiver is a critical role that many of us have assumed. The problem is that we have not had the support."

Erica Gebel Berg (*host*):
Parvathy, when you got thrust into this did you find any specific training or educational programs that were available to help you as a caregiver with the skills and the knowledge that all of a sudden you needed to take care of your family?

Parvathy Krishnan:
I wish. I even did a whole lot of research on this. I asked "Are there resource books or are there guides?" When I do presentations, I actually show a slide of all the parenting books that exist on the market, and the most popular ones that talk about how to raise your child, how to be pregnant, how to do this, and how to do that. There are not very many books on how to take care of your child when everything is broken, or how to spend months in the hospital and not go crazy when you are trying to save your child. You are trying to save your house, your marriage, and possibly your other child. I think the biggest blessing and revolution that has now happened for rare diseases, and specifically for caregivers in the rare disease space, is the explosion of social media. The connections we have made through social media. We have found people in our own community when our physicians and amazing research teams could not find other families with this condition as there are less than 200 people in the world diagnosed with it and only 50 or so still alive. When they could not find them, we could go to Facebook or Twitter and find scientists. We could go to Facebook and find other families with the condition. We all have different children with different cancers, but the one thing that we all have in common is the isolation, the frustrations, the exhaustion, and the similarities in testing protocols. Knowing that someone is out there has been the biggest lesson. It is not all captivated in a book but it is definitely life lessons that have been the most impactful.

Right now there is an amazing wealth of podcasts that are available. My favorite, *'Once Upon A Gene'*, is always there and talks about life with a rare disease. There is a whole channel on Amazon that showcases rare disease movies. Now granted, it is not a movie on my condition or my child's condition, but it definitely shows me that other families go through these experiences. While we are all very different, our similarities are so striking when it comes to our needs and our wants and our common frustrations and needs of the caregiver and the patient community.

Erica Gebel Berg (*host*):
Amy, since you brought up the technology and social media aspect of this, I wanted to ask, in what ways can technology and telehealth services be harnessed to support caregivers? I was going to say in remote or underserved areas, but it sounds as though most caregivers in the rare disease community at least feel remote and underserved.

Amy Jayne McKnight:
I think that has been captured really well by my colleagues and very eloquently. Caring 24/7 for one or more family members with really complex care needs can make it difficult to leave the house to even get your shopping or your groceries. Caregivers that are struggling to find time to get a cup of coffee are arguably the ones who need the most support, yet they are the most difficult to include in research that aims to identify how to best support them. There is a lot of work to be done but at a really basic level, using technology enables people to access resources as and when they need them. When they have five minutes, they can go online and look for those scientists or look for the information about their disease. The difficulty is that there is so much information out there, how do you know what is accurate? How do you know what to trust? I think we could help by developing some online information hubs that are one-stop shops that signpost people to where to get explicit help when they need it, whether that is with broken equipment or whether that is through peer support. I think telehealth has enabled home health monitoring, meaning we no longer need to travel for hours and hours to get to a hospital for a short appointment. So many of the devices, whether it is a watch or a ring or your complex spirometry breathing equipment, now upload the health results online from what you are using at home from day to day. Technology is really useful to help minimize geographical and social barriers, helping people get in touch across the world for both peer and professional support.

"Caregivers that are struggling to find time to get a cup of coffee are arguably the ones who need the most support, yet they are the most difficult to include in research that aims to identify how to best support them."

"Technology is really useful to help minimize geographical and social barriers, helping people get in touch across the world for both peer and professional support."

Erica Gebel Berg (*host*):
Maria, in a related question, how can caregivers of rare disease patients connect and share experiences and resources effectively, especially when they are geographically located in different areas?

Maria Della Rocca:
Well, as some of the other panelists have mentioned, there are support organizations and patient advocacy groups. So, even if there is not one specifically for the disease of your child or the person you are caring for, there are general organizations out there that can provide support to those living with rare diseases or caring for those living with rare diseases. There is Global Genes, NORD, and EURORDIS, so there are different ones out there which give people the opportunity to connect with each other. There are disease specific patient advocacy groups, as others have mentioned, with some of them offering in-person support groups that meet weekly or biweekly. There are also the online

support groups that meet through Zoom or Google or through social media. Private Facebook groups, different forums and platforms are now much more readily available than they were previously. There is also the opportunity to come together at conferences from all around the world, if there is a conference on your specific disease or an umbrella group that is coming together for the similar symptoms or groups of diseases. So, I think that there are many more options now in terms of how people can connect. Post-pandemic, there is a lot more technology that is available that allows people to connect from all parts of the world.

Erica Gebel Berg (*host*):

Alicia, if we switch gears to outside of the rare disease space, what are some innovative approaches or programs that have been successful in supporting caregivers that people in the rare disease space might benefit from learning about?

Catherine Alicia Georges:

I think some of our previous speakers have really clearly defined some of those. Peer support is an excellent one, particularly for older adults with any kinds of dementia, which has worked. We have heard, at least in my work in both caregiving and as a nurse and in community-based organizations, that these have been very helpful. I myself went online and participated in a support group. You think you are the only one sometimes because the burden is so heavy, but then you find out that you are not and other people give you suggestions. They just talk. Sometimes just talking to people and understanding that they are going through the same thing can be so helpful. Then, we have so many agencies. There is a colleague of mine who works out of Emory University called Dr. Fayron Epps, who has what she calls a faith-based research lab for Black caregivers, based in churches. She helps the leaders in those churches to begin to understand what it is that their parishioners may need and in the development of caring for persons who maybe have Alzheimer's, who happen to be in the African American community. I must say that diseases like sickle cell disease being classified as a rare disease has made it harder to find support groups. Therefore I think community-based programs are excellent. There are innovative ones across the country. If you are looking for older adults, the Elizabeth Dole Foundation has excellent services. AARP has excellent services. There are free respite services. I listened to Parvathy and Amy and Maria talk about the burden of rare disease, but what about respite? People who are burdened need some relief. So having some respite care is important.

> ***"Sometimes just talking to people and understanding that they are going through the same thing can be so helpful."***

Also, in regards to children or persons with rare diseases, the National Health Services in the UK has champions for dementia. Maybe we need to have champions in hospitals where people like Parvathy have been with her child for weeks and months and have those kinds of healthcare professionals who become champions for persons with rare diseases. That way you have somebody right within the hospital setting who can anticipate some of your needs and be there alongside you, because it is a lonely place when you are there by yourself caring for children with a rare disease. There are a number of places and we should use the media, we should use technology, including FaceTime, Facebook, Instagram, and maybe TikTok. We need those kinds of programs that will reach a large audience and for people to understand what is going on in this whole caregiving journey.

Erica Gebel Berg (*host*):

Amy, I've read your study, Needs of informal caregivers of people with rare disease: a rapid review of the literature, *and those are the people I think we are talking about here today. Can you elaborate on the concept of caregiver burden and how it was discussed in the literature you reviewed and talk about the main factors, from an academic perspective, which contribute to caregiver burden?*

Amy Jayne McKnight:

Being a caregiver is often described as a privilege and brings a sense of satisfaction to people who are helping their loved ones live as independently as possible. But caring for somebody with a rare disease is often emotionally and physically draining. As we have heard, it is 24 hours a day, seven days a week, and can negatively impact a caregiver's personal health and wider family life. It is often unpaid. There is no respite, particularly after services were severely limited during the COVID-19 pandemic. We find many caregiver juggle looking after complex health needs and complex medical equipment. There is often more than one family member affected by rare conditions. The parents or other family members must often become experts in the disease. They are having to research about each condition, each side effect, and each treatment. They are acting as advocates and they are acting as medical navigators. I like the term medical parent. I had not genuinely heard that before, but it is so true.

I think the other thing to remember is that managing living with a disability often means a higher cost of living. You have got extra washing and extra heating. All of that complex medical equipment is powered by electricity. There is a loss of paid work, resulting in financial concerns. It is really difficult to plan anything. Your plans change at short notice. Someone becomes ill or you have a very short notice hospital appointment. Caregivers rarely have a full night's sleep. Many people are interrupted for an hour, two hours or every couple of hours. Healthcare professionals are rarely well informed about the conditions. It is frankly exhausting, not only physically but emotionally, watching friends and family live through some really unpleasant conditions.

> ***"I think the other thing to remember is that managing living with a disability often means a higher cost of living."***

Erica Gebel Berg (*host*):
Parvathy, we have talked a little about the financial aspects of caregiving. Are there resources specific to caregivers of rare diseases for dealing with the financial toll of these conditions?

Parvathy Krishnan:
We are at that conjuncture where, in our case, my daughter passed away but my son who is still living has a cancer predisposition syndrome, which is ultra rare. He is the only one in the world with this particular gene mutation. It pains me to even say this, but the reality is that I am thankful that we are in the oncology space because there is definitely more support, more respite and more understanding of the caregiver burden, which is severely lacking in the rare disease space. We do have organizations that come forth and support us. We travel every three to six weeks for a clinical trial. We travel from North Carolina to Boston, which is where my son receives care. We are thankful for insurance that covers the care that he gets at the hospital. However, we do not have anyone that supports us for the travel, the expenses, the medical equipment that we have to take with us, or for running a house while we are also providing our child with the care that he needs. At one point of time, each parent would take one child in our house and go to a different institution, all while also having full-time jobs and taking care of our children in the hospital, 24/7. There are a lot of financial holes that form when you are doing this and it is not something that is finite. Unfortunately, in the rare disease world, it is a marathon. It is not a sprint. Therefore the cumulative damage of the financial burden that happens to rare disease families is pretty chronic. It takes a lot for a family to even ask for help because it is not about not wanting to ask for help, but the paperwork that is involved is in addition to everything else that we do. Organizations do exist. There are wonderful organizations like the one that supports us. It is called Children's Flight of Hope and covers our travel costs when we have to go from one state to another. That is a huge barrier that is lifted for a family like ours. We do not get support from clinical trials because it is an off-label use that they are using for my child. So there are a lot of positives and a lot of negatives. Is there support? There is. Is there enough? Absolutely not. There are over 10,000 rare diseases. The more ultra rare you get, the further away you are from the number of people diagnosed with the condition and the more isolated you are with the support and the resources that you need.

"Unfortunately, in the rare disease world, it is a marathon. It is not a sprint. Therefore the cumulative damage of the financial burden that happens to rare disease families is pretty chronic."

Erica Gebel Berg (*host*):
Maria, how can healthcare systems and healthcare professionals better collaborate with caregivers to ensure a more holistic approach to patient care? How can the healthcare system play a role in that?

Maria Della Rocca:
As we know, rare diseases are complex, and the care involves a number of different specialists, nurses, genetic counselors, social workers, laboratories and more. It is critical to have a united team approach adopted. Unfortunately, there are many healthcare systems that are highly fragmented, such as the one we have here in the United States. Many healthcare professionals believe that coordinated care and working together is critical in order to provide the best care for patients. However, with the way the system is structured today, it typically all falls on the caregiver to take on the role of coordinating the care, adding yet another responsibility to that specific person. Sometimes a caregiver may be fortunate and be able to work with a case manager who could take on some of that responsibility and alleviate some of the potential stress.

Patient organizations are a great resource, when available, on how to successfully coordinate care across clinicians, centers, hospitals, and other service providers. Some of the tips to consider when assembling a quality healthcare team and coordinating that care might include ensuring that all the medical records are easily accessible to all the doctors in the centers, as well as the caregivers. It might also include making sure that those healthcare providers are available to provide advice and guidance 24 hours a day. There has to be a commitment among all of the different team members for good communication. Creating a care coordination plan in conjunction with a medical care team can help improve outcomes and foster collaboration between the providers, as well as empower the caregiver to be part of that decision making process in the care management. The care coordination plan consists of organizing patient activities and sharing information with all the team members, and may involve setting up a schedule for healthcare provider visits, medications and treatments.

It may also consist of providing resources to find local services or providers, referrals to specialists and healthcare professionals, community resources and case managers who can assist with finding caring services, as well as getting insurance approval for caring services and helping to coordinate the care among all the various providers. I think having a care coordination plan where you are working very closely with the different care providers is definitely a way we can to help make sure that we are working more closely together and it is a more holistic approach for patient care.

Erica Gebel Berg (*host*):
Amy, we talked a little bit about fragmented US healthcare. I am curious, is it different where you are? Are caregivers factored into this holistic care model we were just talking about in Belfast?

Amy Jayne McKnight:
Unfortunately not. We see the same thing no matter where we are across the world. It is a consistently repeated message. People struggle to put a name to their disease and then they struggle to get the coordinated care once they have the name or many people will never actually get a name for their disease. I think what is really important is the need to bring caregiver into the conversation about developing that care plan. It is not about the doctors telling you what to do, as most of the time they do not know what

to do. It is about working with the specialist nurses, the doctors, the physiotherapists, the occupational therapists, the education specialists, and most importantly, the people who are living every day with that rare disease to develop a holistic approach to care for everyone involved: the patient and their caregivers.

Erica Gebel Berg (*host*):

Alicia, I was wondering if you could share with us some examples of any policies or initiatives at local, national, or international levels that have positively impacted caregivers of individuals either with rare diseases or more generally any disease. Are there policies or initiatives on a government level and things that advocates could be striving for?

Catherine Alicia Georges:

I do not know why but it seems as though folks, and I am talking about healthcare professionals within institutions, are unaware of the CARE Act. Not CARES, but CARE Act, which is the Caregiver Advise, Record and Enable Act. It is so important when one is hospitalized that the caregiver is given information, that knowledge is shared, and that skills may be taught so that when that person leaves the institution, they can transition home having some knowledge and skills about what it is that they need in order to care for that patient. That is applicable to rare diseases and chronic diseases, and it is so important. It is an act that has been passed in over forty states in the United States. Then, of course, you all know about NORD's various programs where they have worked with other organizations across the world. The other one, right here in the United States, which has evolved over time is the National Family Caregiver Support Program. Now, that is money that is given to states and the states are the ones that give grants. It is not just in the continent of the United States, but also in the territories, but it tends to focus on older adults. Some of it is a lack of information being shared with the public so that people are not aware. Some of the advocacy organizations do know about it and will go after it.

I have to also give a shout out to the RAISE Act and the Family Caregiving Advisory Council, which was an act of Congress and signed by one of our former presidents. The fact that we on the council were able to give recommendations to the Secretary of Health and Human Services has lead to the start of changes within federal agencies of the US government, where those agencies have been charged to look at their policies and initiatives and ensure that they are supportive to family caregivers. The agency that deals with children has been charged to look and see what they can do and must do and the services that they provide. Again, that is the Federal Government and everything is local, so you still have to go through your states to get some of the services that one may need. But that is a great start. I think that this country is finally beginning to understand what it means for family caregiving. There is $600 billion of unpaid caregiving in this country. The government does not have to take that on but they need to assist families who have to go through giving care. This includes the loss of income, like Parvathy said, money for traveling, and all those financial implications that families have in caring for someone with a rare disease or chronic illness.

Erica Gebel Berg (*host*):

Maria, Amy, Parvathy, are there any policies or initiatives that are currently in progress, wherever you are, that our audience might not be aware of and might be interested in knowing about?

Parvathy Krishnan:

I will add that there is a fantastic initiative by the American Board of Pediatrics Foundation on mental health and behavioral mental health and it is not just for patients in the rare disease space, but also for medically complex patients or children who receive specialized care. They are training residents and attending physicians within certain centers that they have picked and they are doing a very phenomenal and specific task of trying to train these specialized professionals on how to ask patients and families about their mental health and how to provide them with support services should they exhibit that they have some issues or if they would like more help. I think that in itself is the start of a very important series of positive changes that are happening within the health care system, because if they are not even being asked questions like, "How are you? Is there something going on? How can we help?", while they are actively receiving care from that clinic, it is going to be very hard for the rest of the ecosystem to then fall into place. So a huge kudos and shout out to the American Board of Pediatrics Foundation for the work that they are doing on mental health and how to improve it, not just for the pediatric patient, but for the family as a whole.

Maria Della Rocca:

Just to piggyback on that, we have a program here at Global Genes called the Rare Compassion Program, which aims to educate medical students. This program reaches the next generation of doctors that will be out there working and interfacing with rare disease patients and their families early on. It gives them the experience of speaking with patients and learning about their lived experience, as well as being able to be compassionate and, as Parvathy mentioned, being able to detect and recognize when there may be some mental health issues at play that need to be addressed. It looks like there are definitely areas that are being addressed across the board and it is really exciting to see what it will to bring to the next generation.

Erica Gebel Berg (*host*):

Amy, I was wondering if you could share with us what you have learned about the mental health toll of caregiving in the rare disease space and have you found anything that can help alleviate that? Is there anything we can learn from your research on mental health for rare disease caregivers?

Amy Jayne McKnight:

Absolutely. We have done a lot of research trying to tease out that mental health question. For every survey, focus group and interview we have had, every single participant has responded to say that caregiving has had a negative impact on their mental health. With the best will in the world, they are not supported to

care to the best of their ability while also looking after their self-care and managing all of the other responsibilities that go along with that. I think one thing that comes through so clearly to me is that there is so much that healthcare professionals and institutions and voluntary advocacy support groups can do to actually help support our caregivers. That may be developing something as simple as an online support tool that helps people get explicit advice to answer explicit questions such as, "Your oxygen respiratory machine has broken in the middle of the night. What do you do? Where do you get support? Who do you contact to get more accurate, validated information about the disease?" So, not just through a Google search, but being able to know where to go to get the right information and how to put people in touch with the right professionals. There are even really simple things, if we are thinking about supporting the family unit and improving their mental health, such as more information about accessible leisure facilities and where can you go with a wheelchair? There is no point living next door to a forest park if there is a stile that a wheelchair cannot get through or if there is a height restriction on your car park, which means that your wheelchair accessible vehicle cannot fit under that height restriction.

Peer support is such a valuable tool. Is there a better way in which we can put people in contact with each other to minimize the geographical and social isolation that many people feel that really contributes towards the negative mental health? I think if we can improve things like providing regular respite facilities, flexible employment opportunities, and fair pay for those who provide care for their families and friends, then it would do so much to help alleviate those mental health challenges for people who are giving care.

"For every survey, focus group and interview we have had, every single participant has responded to say that caregiving has had a negative impact on their mental health."

"I think if we can improve things like providing regular respite facilities, flexible employment opportunities, and fair pay for those who provide care for their families and friends, then it would do so much to help alleviate those mental health challenges for people who are giving care."

Erica Gebel Berg (*host*):

This has come up several times, the question of "Where do you go to get good information about these issues?" Do we have an answer? Everyone begins with a Google search, but once we are done with that what is the next step to accessing that good information? Maria, do you have thoughts on that?

Maria Della Rocca:

There are different organizations that provide that type of support, for instance we have our RARE Concierge program, which is available for anyone in the rare disease community. We get inquiries from people who are in the undiagnosed journey or have been newly diagnosed, as well as from people who have been diagnosed or have other specific questions or are experiencing a challenging time and are looking for resources. Sometimes, you do not know where to begin. You just need someone to kind of anticipate those initial questions in order to get you exposed to that information or those resources that might be available. There are other organizations, like NORD. For people who might be in Europe, EURORDIS has resources too for the different organizations and the different European countries. So that is one place to start. You can start with some of those programs, but if there is a disease specific organization, that is a great place to start. You come together with people who have gone through that experience before and you can take a lot of their lessons learned. I think everyone here has mentioned that sometimes just knowing that someone else has been through that experience can be very comforting.

"Sometimes, you do not know where to begin. You just need someone to kind of anticipate those initial questions in order to get you exposed to that information or those resources that might be available."

Amy Jayne McKnight:

If I could just jump in on that, for our European colleagues we have the RareConnect program that helps people get in touch with each other. Another really good resource is Orphanet, which does provide links to expertly curated information about a range of rare diseases.

Erica Gebel Berg (*host*):

Alicia, I was wondering if you could talk a little bit about how employers in workplaces can be more supportive to caregivers, especially considering that diseases are unpredictable and require a level of flexibility. Is there something you have learned about how these workplaces can be more supportive and is there advocacy efforts that we could be engaging in to make change where needed?

Catherine Alicia Georges:

There are some employers who already have them as part of the benefits. You do not have to go and submit a slip and cry and beg to have time off, but you will automatically be given the time off for family caregiving. That is critical as you do not know when it will happen, so as soon as it happens that will occur. That has been increasing but not as much as we would hope it would. Beyond the Family and Medical Leave Act (FMLA), we need to have organizations that are open and ready to put aside some time where employees can be given the opportunity to care for family members if they need to on an emergency basis.

The other thing that employers do is offer resources on wellness and how to eat right. We could also have focus groups at work for those who are in the caregiving space to help with their mental health issues, to help them learn how to relieve stress, to learn about financial workshops and to help them receive assistance, because there are a number of things available in some states, such as tax credits that you can get for caregiving. We need to have employers who are really committed to making sure that they want their employees to be ready and willing to work. The other thing that they can do is they can rethink how people are working. We learned from the COVID-19 pandemic that you do not have to sit in an office to be productive, depending on what you do. For some of us who are direct providers, you must go to work because you have a patient that you must interact with, but there are lots of things that employers can do.

Erica Gebel Berg (*host*):

Amy, could you talk about research initiatives that are currently underway that you are engaging in to better understand and address the needs of caregivers in the rare disease community?

Amy Jayne McKnight:

Having spent the last hour talking about so many challenges, I am delighted to say that there actually are lots of initiatives emerging as the need to support caregivers is being increasingly recognized. As part of the global burden of disease survey, there is now a specific component looking at the burden of rare disease. We have recently received funding to work with rare disease caregivers to co-develop an online support tool that addresses many of the shared and unique challenges that they do experience. So, there is a lot going on. It is a case of watch this space.

Erica Gebel Berg (host):

Parvathy, how have you or how can caregivers balance their caregiving responsibilities with their own personal and professional life?

Parvathy Krishnan:

That is a hard one and it is often a balance. Because if I have to drop everything to care for my child who is having a bleeding disorder and is in the hospital, then that is what I do. I definitely need to either be self-employed or work for an organization that is extremely understanding of our situation. To add to Alicia's point, COVID-19 actually helped because not only did it open up telehealth but it also opened up remote work, which I think has been a blessing in disguise for rare disease families. I think the most important concern is harder to alleviate because everybody worries about the financial burden of living with a rare disease or caring for someone with a rare disease. Since that is a very hard burden to eliminate by saying, "just find a job or work", the other things that we can work on is how to keep ourselves stable and mentally prepared to deal with the caregiving needs. As Amy said, it is very exhausting and it is nonstop. While it is the best thing that has happened to us, as obviously caring for our children is the most rewarding part of our life; it is also the most exhausting part of our life. Therefore I think that trying to understand and accept it and coming to terms with the fact that this is our new normal is one of the most impactful ways that you can provide yourself with some self sympathy and kindness. I think those are very simple things that can be of tremendous impact in the journey of a person providing care for someone with a rare disease. While it sounds very simple, it requires a lot of therapy and a lot of support and an ecosystem of not just family or friends, but also the medical system, the insurance system and our community as a whole. We have tried to educate our local community that it is not a sprint, it is a marathon. Unlike other cancers, my child's cancer will never go away. He has a genetic condition so he is going to keep getting cancers throughout this life. I think part of self-care for me has been increasing awareness. If just one other person understands our struggle, maybe they will be kind to other parents like us and provide the support that we need.

I know in addition to everything else that we do, unfortunately, part of our responsibility as a rare disease caregiver has also included education and awareness to either our nuclear community or the larger community about our challenges and our successes as well, because I think none of us would be here talking about all of this if we had not had some successes and some support. For me personally, self-care is talking about our experiences so that it can help others not go through the same things and make it a little bit easier. I think COVID-19 changed the narrative on what self-care is. We do not have time to go get a pedicure. So that is not the self-care that works for me. But being on the patient family advisory board at my local hospital actually fills my cup in a better way, as I feel like I can bring that change that will lead to improvements for when my child gets readmitted to a hospital.

"I think part of self-care for me has been increasing awareness. If just one other person understands our struggle, maybe they will be kind to other parents like us and provide the support that we need."

Erica Gebel Berg (*host*):

Thank you. Unfortunately, we will have to stop there as we have run out of time. It has been a delight talking with you all. Thank you once again to our panel and to Foundation Ipsen for enabling this conversation through their kind sponsorship.

Advocacy in rare disease: Driving technology advances

By many measures, this is a golden age of drug discovery, particularly for rare diseases. In 2022, more than half of the novel drugs approved by the U. S. Food and Drug Administration were for patients with rare disease. Many of these treatments represent modalities at the cutting edge of medicine. With genomics advances offering pathways to personalized medicine and artificial intelligence transforming pharmaceutical research, people with rare diseases have reason to hope. Yet, in too many cases, conditions remain without diagnostic or treatment options, so advocates continue to make a case for technology advancements that could bring about new therapies. At the same time, ensuring patients have equitable access to the latest advances across the globe remains a challenge as well.

In this Science Webinar, participants will:

- Explore the pivotal role technology play in advancing diagnostic and treatment options for rare diseases,
- Hear about the latest breakthroughs in genomics, cell and gene therapies, and digital innovations in rare disease,
- Learn how advocates are ensuring advances in rare disease technology reach people who need them.

Panelists

Simon Alfano
McKinsey & Company, Boston, MA

Karin Hoelzer, D.V.M., Ph.D.
National Organization for Rare Disorders
Washington, DC

Heidi L. Rehm, Ph.D., FACMG
Massachusetts General Hospital, Boston, MA

Léon van Wouwe
Volv Global, Epalinges, Switzerland

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

The Conversation

Erika Berg (*host*):
Hello everyone, and welcome to the webinar entitled Driving Technology Advances. I am Erika Berg, Director and Senior Editor for Custom Publishing at Science, and I will be the moderator of this discussion. Today, we will be having a conversation about the intersection of advocacy and technology.

By many measures, this is a golden age of drug discovery, particularly for rare diseases. In 2022, more than half the novel drugs approved by the US Food and Drug Administration were for patients with rare diseases. Many of these treatments represent modalities at the cutting edge of medicine. With genomics advances offering pathways to personalized medicine and artificial intelligence transforming pharmaceutical research, people with rare diseases have reason to hope. Yet in too many cases, conditions remain without diagnostic or treatment options. So, advocates continue to make a case for technology advancements that could bring about new therapies. At the same time, ensuring patients have equitable access to the latest advances across the globe remains a challenge as well.

I would now like to take the opportunity to welcome our excellent panel today. I will give each of them a chance to say hello and introduce themselves.

Karin Hoelzer:
I am Karin Holzer and by training I am an infectious disease epidemiologist and a veterinarian. Early in my career, I served as a risk analyst modeler and set up a health data analytics division during COVID. In my current job, I direct policy and regulatory affairs for NORD, an umbrella organization for patient advocacy organizations in the rare disease space. I am thrilled to be here today.

Léon Van Wouwe:
My name is Léon van Wouwe. I am a medical biologist by training and I have spent many years working in the pharmaceutical industry in operational clinical drug development. Having become slightly frustrated with the repeated issues that we saw there, not quite reflecting the true patient populations in the clinical drug development, I decided to join the service industry, where I am looking to build bridges between real-world data through technology into clinical development and patient care.

Heidi L. Rehm:
My background is part of the Center for Genomic Medicine at Mass General Hospital. I am also the Chief Genomics Officer where I am involved in rolling out genomic medicine to the patient populations within our healthcare system. I also work at the Broad Institute where I am the Co-director of the Medical and Population

Genetics Program and do a lot of work in building resources to support genomics and rare disease gene discovery and diagnosis of patients. I also am the Medical and Clinical Lab Director at the Broad Clinical Laboratories, where I am involved in clinical diagnostics to enable patients to get diagnoses and predict onset of disease.

Simon Alfano:
I am an associate partner with McKinsey in our Boston office and co-lead our rare disease group within our life sciences practice. I spent most of my time with small and mid-sized biotech companies, helping them launch and commercialize new rare disease therapies and bringing them to patients in need. I am looking forward to the discussion today with everyone.

Erika Berg (*host*):
I am going to give my first question to Karin. Despite so much progress that has been happening with rare disease technologies and medicine in general, why do so many rare conditions still lack diagnostic or treatment options? And what are the primary challenges in addressing these gaps?

Karin Hoelzer:
As you said, we have come a long way. We have a lot more therapies today than we had 40 years ago, but we still know that of the more than 7,000 rare diseases that are out there, the vast majority have no treatment options. Many of our patients have to go through a diagnostic odyssey of five to seven years until they arrive at the right diagnosis, which is horrific for the patients and their families. One of the key reasons for these challenges is data. Scarcity of data around the natural history of the diseases and scarcity of data as we have small patient populations that make it very hard to run clinical trials. We have diseases that are very heterogeneous in how they manifest, which means that they can look very different from one patient to another, which makes it very hard to study. It is very hard to find patients because of underdiagnosis and because care in the US is decentralized and the data systems are not centralized. We have key challenges in the fact that the natural history of disease and how diseases progress is not well understood. Access to diagnostics as well as diagnostic testing is still limited. More than 80% of all rare diseases have a genetic basis. With the advances in genetics and genomics, we are seeing some improvement in diagnostics, but access to these new therapies is still a big challenge. In short, data is at the center of many of the rules that we are experiencing.

"We have a lot more therapies today than we had 40 years ago, but we still know that of the more than 7,000 rare diseases that are out there, the vast majority have no treatment options. Many of our patients have to go through a diagnostic odyssey of five to seven years until they arrive at the right diagnosis, which is horrific for the patients and their families."

Léon Van Wouwe:
I think the summary that you gave, Karin, resonated and it was reflected in a workshop the Volv team did at the World Orphan Drug Congress in Barcelona earlier this month. Those were precisely the issues that came across. It is the lack of understanding of the disease, and not just with researchers but also with clinicians, which is the fundamental issue when it comes to why so many patients do not get diagnosed. There was recently an article about Alpha-1 antitrypsin deficiency (AATD), where an around 90% underdiagnosis is expected or suspected. The typically really small patient populations are making it difficult to do these kinds of trials.

Karin Hoelzer:
And we are still recognizing new rare diseases every day. So, there is a lot we do not know.

Léon Van Wouwe:
I think another major point to acknowledge is that drug development is a risky business. What we see is a typical phenomenon of pipeline herding. We know in the rare disease space a fair amount about lysosomal storage disorders, so a lot of what we see in terms of drug development happens in that space. We see that in the larger industry as well, where about two thirds of the R&D budgets go towards oncology. It is a known field with a manageable risk. I think figuring out how we can de-risk drug development is one of the key challenges.

Erika Berg (*host*):
My next question is for Heidi. How have advances in life sciences, particularly genomics but feel free to branch out from there, played a pivotal role in advancing diagnostic and treatment options for rare diseases to date and thinking about in the future as well?

Heidi L. Rehm:
There have been major advances in genomic technologies that have really aided in diagnosing patients. One of the key ones is in sequencing technologies and the cost of sequencing an individual's genome. It used to be that a physician had to make a really good guess at what the patient's clinical diagnosis was and then test the gene or genes that were relevant to that diagnosis, because the cost of sequencing genes was so high. Nowadays, sequencing is cheap enough that with a few hundred dollars we can sequence an individual's entire genome, which means we do not have to make a guess in advance as to what exactly the basis of their disorder may be. We can sequence every gene, including genes that have never been implicated in disease, and thereby discover novel causes of disease. So the technology in terms of sequencing development has allowed us to really push the field in terms of making diagnoses.

That said, the gaps that were mentioned earlier are still there, but more on the side of how we interpret the data, not in the actual generation of it. Therefore, we are still working to advance the analytical approaches so that we can analyze genomes and interpret whether a variant may be leading to disease or if that variant

is actually benign and does not impact an individual's health. A lot of the current focus is on adjunct technologies to help us interpret the data that we find in individuals as well as ensure that we are sharing that data very broadly so that we can understand it in aggregate, which is always more powerful than looking at one genome at a time.

> ***"Nowadays, sequencing is cheap enough that with a few hundred dollars we can sequence an individual's entire genome, which means we do not have to make a guess in advance as to what exactly the basis of their disorder may be. We can sequence every gene, including genes that have never been implicated in disease, and thereby discover novel causes of disease."***

Karin Hoelzer:
One key concern from our perspective is the representativeness of the data that is available for the interpretation. By understanding that we have dire health inequities in this country and that any genetic test is only as good as the data on which it is based on, we must try to make sure that the data sets are appropriately reflective of the whole patient population.

Heidi L. Rehm:
That is absolutely correct. I will just add that we need data from every corner of the world to help inform our understanding of the causes of rare diseases. Through the Global Alliance for Genomics and Health and other efforts, we are really working to gather data from all around the world because information in one population will help us interpret data in another population and also create equities in terms of everyone being able to benefit from diagnoses.

Léon Van Wouwe:
I think notwithstanding the great benefits of the advances in newborn screening technologies and genetic testing in general, what we really do still need to do is build the bridges between genotype and phenotype because, particularly in rare diseases, the symptomatic penetration of gene defects is very diffused, at least to the type of heterogeneity that both Karin and Heidi have referred to earlier.

Erika Berg (*host*):
Simon, I was wondering if you could talk about how digital innovation, such as artificial intelligence, has played a role in advancing diagnostic and treatment options for rare diseases.

Simon Alfano:
Yes and think of it as applications along the full continuum from understanding to diagnosing disease. Heidi already talked about understanding the different genetic conditions and markers of specific rare diseases and also the heterogeneity of diseases. Then there is developing new therapeutics for those known diseases where you can also use artificial intelligence to basically understand and identify relatively quickly, for known diseases with known genetic markers, whether there could be a potential mechanism of action that could work and be brought into clinical development. Then as we move along the journey of a rare disease, for known rare diseases, AI can then also help really understand where patients are and help identify them faster and also identify previously undiagnosed patients. We could maybe also talk a bit more about advanced patient finding. There have been great advances made in the last years around better data landscape, in particular in the US where more data is just available through claims data, EMR data and other data sources. Then there is also the ability to combine them and tokenize them so that you can basically build end-to-end patient views across different data sources, that enable you then to predict patients and also predict where patients may have an underlying disease that are not yet known. We recently partnered with a nonprofit for a neurologic pediatric disorder and only 20% of the patients that have been predicted by the model have already been diagnosed based on the available claims data. This data can help to then also inform where to invest into specialist education creating centers of excellence. You also see where health inequities play into the diagnosis rate based on distance to specialists, based on income and other factors, and help better close those gaps and also educate and inform specialists.

Léon Van Wouwe:
I can fully build on that Simon. This is exactly the field that Volv, as a data science company, works in. We work with large scale, electronic medical record data or electronic claims data, and it is exactly those points that you bring up, Simon, which we focus on. The first base is to find those patients that do not get diagnosed typically, and there are a lot of them. From the work that we have done, and we have done projects in a variety of rare indications to date, we see that typically there are two to three times more patients that are predicted undiagnosed as there are already diagnosed. So that is a huge number of patients that do not come to diagnosis. The other thing that we are focusing on is all of these rare diseases are progressive in nature, so it is crucially important not just to find them, but to find them earlier. So that is the next area that we are focusing on. If you can do that you can learn an awful lot more about the disease. So that is the third area that Simon referred to. If you can start to map out the natural history of these patients, both the diagnosed and the undiagnosed, and compare them, you can really start to distill out biological markers of disease earlier in the disease pathway, which can help you on your way towards drug development. So these are really the core elements of what we focus on.

Karin Hoelzer:
If I may add from our perspective, there are two additional areas where we are really looking to AI and some of the new data analysis techniques for rare diseases. One is around control around clinical trials. We have very small patient populations so finding patients is really hard and our patients are not particularly excited about being in placebo-controlled trials. So, digital trends and synthetic data have a tremendous potential to either reduce the time that patients have to be on placebo, reduce the number of patients that have to be on placebo or potentially in the future to

even eliminate the need for this. So there is a tremendous power there. The other area is around drug repurposing. Many drugs that are already on the market where we already have safety data could potentially work for additional diseases. AI is really good at pattern matching and pattern finding, so there are a number of startups right now that are trying to use AI to predict new uses for existing therapies that would hopefully significantly cut down the time to market and allow so many more of our rare diseases to find effective therapies.

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Léon Van Wouwe:
I am glad you are bringing up the topic of the external controls. It was one of the things that came up in the panel session at the World Orphan Drug Congress, where one of the panelists asked how do we really make much better use of all the real-world data that is out there? The patient populations are truly very small and they are very sparse and spread out in rare disease. So that is the real challenge. It is quite good that actually the FDA guidance for industry is to use natural history studies more in orphan drug development. It is absolutely valid and we need to work towards doing that much better. But it is not straightforward because there are big confounder effects, particularly when you work with small patient populations. That becomes a real issue. A really good example is if you have patients with asthma that experience an acute respiratory crisis, they tend to do better in terms of outcomes in the hospital. This is counterintuitive, as it is not because of asthma that they do better, it is because they have asthma that they are routed to a much higher care level straight away. So, these are the kind of confounder effects that you must be extremely careful of. That is another area of research that Volv is looking into.

Karin Hoelzer:
If I might give a slightly different spin on this topic, a lot of patient groups in the rare space are running their own registries and running their own natural history studies. We at NORD run about 40 on our platform for different patient advocacy groups. There is a tremendous learning curve, with setting up data use agreements, understanding how to properly analyze the data, and how to structure the surveys. Thankfully, we have some funding from the FDA to work with the patient communities to get them what we call "research ready", but that is another tremendous need. We want to empower patients and patient groups to collect their own data, but they need to know how to make it fit for regulatory purposes.

Erika Berg (*host*):
I think Léon, you already provided one example, but I am wondering if there are examples of these cutting edge approaches to rare disease that are already in play that any of you would like to share. I think you were talking about the one example, but are there other examples that could make these advances more solid and give us a sense of where we are right now in terms of actually using some of these cutting edge technologies?

Léon Van Wouwe:
I am working for Volv and we are a commercial organization. We work with clients in the pharmaceutical industry, specifically on these challenges. The company was formed around the true business problem where a pharmaceutical client has a drug in market, they know it is a four in a million disease, and they can only ever find one. So where are the other three? So that is what underpinned the company. What Volv is really about is how to make cutting-edge data science applicable and meaningful in the clinical setting for patients, for healthcare communities and for the drug development research setting.

What we really focus on is finding these patients earlier and, as I said, most of our projects indicate that we can find the patients in the first instance anyway. Most of the projects show that we can find two to three times more patients than are already diagnosed. So that is a really significant improvement, but it is not just about finding them. That is not where it stops. The technology here can only take you so far. Ultimately, in the world of medicine, it really is a people-to-people kind of thing, and you are operating in a clinical setting. It is not enough to just flag patients predicted as living with a rare disease that have not yet been diagnosed. It is how do you actually facilitate and enable the clinical system so that action is taken and those patients are sent for confirmatory diagnosis and then get access to care. So that is what we are working on to develop. Other examples are finding, as I mentioned, the progressive diseases earlier and we know that it is possible. So that is a line of research that we are pursuing for our clients. Once you have learned the model to actually find those patients that have not yet received a diagnosis, you want to know how much earlier you can find them. We have data on file now, which is not yet published, for one cardiovascular indication, that if untreated can often lead to sudden cardiac death, where we can potentially find these patients two to four years earlier. We need to look into this in more detail, but this could be before the actual physical change to the heart is measurable to the point that they would actually qualify as having the disease. That could be a real breakthrough.

"It is not enough to just flag patients predicted as living with a rare disease that have not yet been diagnosed. It is how do you actually facilitate and enable the clinical system so that action is taken and those patients are sent for confirmatory diagnosis and then get access to care."

Erika Berg (*host*):
Anyone else have an example they want to share?

Simon Alfano:
Just to add to the technological advances and applications, there are also just very pragmatic applications that you may know from other areas as well. For example, for patients with hemophilia, there are apps that help you understand when your clotting factor levels drop below a certain threshold. It gives caregivers and also patients much more power to understand and manage their disease and also take control of when they, for example, need to take action around re-dosing. Another great way to use technology is through social media, to get educated as a patient, give patient advocacy groups a voice in terms of interacting with patients and educating them, and also just simply providing resources like a specialist finder, where you enter your zip code and understand where specialists are nearby. So I would say that there are many relatively low-key technological advances that can also help patients and caregivers to basically get better access.

Karin Hoelzer:
We have certainly seen COVID-19 being a real transformative force in making a lot of these technologies more accessible, thereby bringing a lot more care into the home. Many of our patients are what we call medically complex, so traveling across the country to see a specialist is a huge deal for many of our patients. With new digital technologies, a lot more care can be provided right in the home or very close to the home, which has really revolutionized patient care. We do need to make sure that insurance coverage does not get in the way. During COVID, access through telehealth and a lot of the digital health technologies has been a lot easier, but making sure that these technologies remain accessible is one of the things we spend a lot of time on from the policy side.

"With new digital technologies, a lot more care can be provided right in the home or very close to the home, which has really revolutionized patient care."

Heidi L. Rehm:
I would also like to add a slightly different perspective around the accessibility issue. No matter how low you can bring down the cost of drugs for rare diseases, it will always be quite high and quite challenging to distribute to everyone in need. We must also think about the fact that for many of these diseases, we can prevent them through basic things like carrier screening, which is widely covered by insurance. But unfortunately, today, most of the patients that get carrier screening do not get it until they are already pregnant and we really need to move population-based carrier screening to before pregnancy as a preconception decision. We now have access to technologies like pre-implantation genetic diagnosis to choose embryos that do not have very severe childhood onset disorders, and therefore to avoid a child ever having those disorders and therefore not suffering from the inequitable access to very expensive drugs. So, it is another element to think about this whole question, more from the side of how can we avoid the need for these drugs at the start and not just once a child is born with a very severe disease asking how can we get access to the drugs?

Erika Berg (*host*):
We are going to talk a bit more about accessibility issues in this part of the discussion. Léon, given the global nature of rare diseases with small patient populations and also just that it is everywhere and people have different levels of access to medical technology. How can we ensure that the latest technological advances are accessible to patients worldwide, regardless of geographic location or economic status?

Léon Van Wouwe:
It touches back on comments that we all have been making earlier. At the end of the day, we operate inside of clinical systems, which are basically run by humans and the technology is not going to solve the fact that humans have constraints. We talked a little bit about what we can do to flag, but that unless you actually optimize the clinical workflow, nothing gets done with the flag. This is the hard reality. We have projects running at the moment where we have been flagging about 163 patients living with either Fabry or Pompe disease in the UK, really good pilot projects, but where the constraint now hits us is in enabling these GP practices to take those patients forward for confirmatory diagnosis. At the moment, there is about a nine-month waiting list in the UK for a referral. Technology is not going to solve that per se, as that is a clinical workflow challenge that we need to all work on together. The other thing is that to apply this all globally, you need to acknowledge that patients are managed inside their own clinical system. That is defined by training from the clinicians or the healthcare professionals. We work in a large electronic healthcare data environment for the work we do but not all the coding systems are the same. Not even all the testing procedures are the same. So if you are looking for signals in all of that healthcare data, you have to acknowledge in which setting you are looking for those signals. A model that we learn in one country cannot simply be deployed in another country for a patient finding. So we have to relearn. That is what we are currently working on to make that more efficient, but not all countries are equally developed. We made a comment about some of the more developmental areas. We will simply not have this large quantity of digital healthcare data in which we can apply the machine learning or AI technology that Volv uses. The same will go for other digital solutions that are being rolled out to help patients in need. That is where it is also about, how can you take these highly complex models and how can you simplify them? So that is another line of research that we are actively pursuing and we have got good reason to believe that it is doable. You do not necessarily, for some diseases, need a highly digitized healthcare environment in order to leverage the technology. If you have learned models about rare diseases in one country where you do have that possibility, you can often take those lessons into other settings. One of the most illustrative examples that I know about is in lipodystrophy. Lipodystrophy is often misdiagnosed as diabetes. It does not look like diabetes, but it is one of the most common misdiagnoses. We have learned from the work that we did that if you ask for one missing parameter, which is often height, you could work out body mass index. So if you have a non-obese patient with high triglycerides, it is probably not diabetes. That helps you point out things like lipodystrophy. Now that is a human deployable question. You do not need AI systems for that but we have had to learn this from large scale data sets using machine learning.

"At the end of the day, we operate inside of clinical systems, which are basically run by humans and the technology is not going to solve the fact that humans have constraints."

Erika Berg (*host*):

Heidi, you talked about how the cost of genomics testing has fallen significantly. Is that to a point where you can build these genomic libraries on a more global scale and get more global data? Where are we when it comes to more comprehensive genomics sequencing?

Heidi L. Rehm:

That is a great question. I think the value of the data in research and scientific endeavors is so high and the cost has come down so much that we are now just starting to see massive populations getting sequencing. So biobanks are popping up all around the world. There is the UK biobank that has been around for quite some time. Now the All of Us research program in the US has enrolled over half a million participants, and we have sequenced almost half a million genomes from that patient population. This is happening at thousands of biobanks around the world. I think as these types of data sets get generated, we will have access to much more rigorous data and also data that is not biased in its ascertainment because we are really just targeting the entire general population and therefore we can derive a lot of insights from systematic medical record collection and systematic genotyping and combine them together. With that said, sometimes these very broad efforts in population biobanking do not always pull in all of the rare disease patients. I think there is a balance of needing very directed recruitment for rare diseases so that we can ensure those populations are collected and the right questions are asked, as Léon and Karin were pointing out, in terms of really defining the natural history of disease, which is critical when you run a clinical trial. I think there is a balance where we are generating a lot more data because the cost of sequencing has come down and we can apply it in very broad ways. That can create great control data sets and population understanding, but we also need a very targeted approach to rare disease diagnosis and characterization to complement that.

"I think the value of the data in research and scientific endeavors is so high and the cost has come down so much that we are now just starting to see massive populations getting sequencing."

Erika Berg (*host*):

I know we have spoken a little bit about there being not enough people around for clinical trials for many of these treatments. Is there any thinking about if you can have more global data that means more people that could feed into clinical trials? Is that something people are thinking about and working towards and what are the barriers to something like that?

Simon Alfano:

What we have seen is in many diseases where you have disproportionate genetic predispositions in certain geographical locations, you often see clinical trial sites in those geographical locations as part of the clinical trial, be it based on certain hereditary traits that lead to geographic clustering or other causes. The other thing that we do see is that over and over again, in diseases where there is a certain understanding and there are therapies developed or available, it is typically a very tight-knit global KOL community where there is a lot of scientific exchange, more so than in primary care or specialty care diseases. So whenever there is a certain threshold of understanding of a disease, you do see a lot of pull from the clinical and scientific community.

The gap is basically the need to branch out into understanding new rare diseases and really developing therapies there as well. I think, Léon, you were alluding to the herding before. If you fast forward the current pipeline, you will see 90% of the therapies by 2028 in areas where you have five or more therapies competing against each other. But there is limited effort in moving into rare diseases that do not yet have a therapy. In these cases, AI can hopefully help unlock solutions based on bringing existing therapies to rare diseases, identifying what opportunities exist to redeploy them or learning from global registries, like Heidi was alluding to, in order to really expand the scope of therapies that are available. Then basically as a follow-up also create those global KOL and patient advocacy communities that really advocate for a more global access to those therapies.

"If you fast forward the current pipeline, you will see 90% of the therapies by 2028 in areas where you have five or more therapies competing against each other. But there is limited effort in moving into rare diseases that do not yet have a therapy."

Karin Hoelzer:

At the more regional scale, we know AI can also be really helpful within the US to help identify where to place sites so that we have equitable access. We know that a number of sponsors have used AI and other big data assessments to be more effective at placing trial sites at places where it is easier for patients with rare diseases to access. We know access challenges are a big barrier. They are one of the reasons why it can be really hard to enroll and keep patients in trials. So I completely agree with everything that Simon said. We must not forget that it is at every scale from the local to the global.

Léon Van Wouwe:

I think those are good points and I can only underline them. Interestingly, the patient populations that are predicted accessible are quite a bit larger than we think they are. In terms of strategically

informing where you are going to perform the studies, there are also lots of new insights that can be discovered using these machine learning technologies. Interestingly, a lot of these patients that are not yet diagnosed are not where you expect them to be. That is one of the reasons why we do not typically find them. I can illustrate with an example. We have done work in acute hepatic porphyria (AHP) and the client had already done a lot of KOL interviewing and everybody agrees that these patients' primary healthcare interaction is with gastroenterology or in the emergency ward when they come in with an acute crisis.

When we did the work for the client organization and we leveraged real-world data through machine learning, we found out that it is only probably about 48% of the patient population with AHP that is primarily being seen in gastroenterology. In another 52%, the primary healthcare interaction is not through gastroenterology. It is not that they are not going to see a gastric specialist, but more often they are being seen by obstetrics and gynecology, neurology, and psychiatry. Now, if everybody is doing the trial program with gastroenterology, and nobody knows about the patients that are seen primarily in these other disciplines, then you are missing out on a lot of patients that you can take forward into development, but there are also a lot of patients that are missing out on these opportunities.

Erika Berg (*host*):

One thing we have not talked a lot about, which people probably think about when they think of advanced technologies in the rare disease space, is cell and gene therapies. Heidi, you have talked about a lot of the emerging treatments being quite expensive. I am wondering if you are referring to the cell and gene therapies and that these modalities that have so much promise also have some challenges and cost associated with them that might make them less accessible. Could you talk a little bit about these emerging therapies and what are the issues of accessibility and how could we make them more accessible so that they could reach more people in the future?

Heidi L. Rehm:

I think the challenges when we talk about rare diseases is there is a small population for each disorder and sometimes, we do not fully understand the prevalence of the disease. Encouraging a pharmaceutical company to actually work on drug development for particular diseases where they are not sure what the market will be is challenging. For a long time, many years ago, we all had hope when gene therapy was first invented, that this was going to just change everything overnight. It did not change everything overnight. I will say that, just in the last few years, we are really starting to see major progress in this area. However, we are still at the early stages where each development is costing a lot of money in terms of the clinical trials.

I think what we now need to start to figure out is where can each of these trials learn from each other in a collective manner so that we can keep the overall costs of drug development lower? I think Léon and Simon can probably comment on this better than I can, because I work more on the diagnostic side than I do on the drug development side, but one thing that we are trying to do to help guide drug development is to actually identify the true prevalence of these disorders from population data. For example, we support one of the largest genomic data sets that are freely accessible through the NOMAD database, where we have 800,000 individuals whose data is sitting in a publicly accessible database in terms of aggregate allele frequencies. So for recessive diseases, we can very accurately predict the population prevalence of those disorders from that data, which then can be shared with patient advocacy groups that are working with pharmaceutical companies to actually inform the true prevalence of those disorders that helps make decisions in these companies as to where there is an actual market for a particular drug or therapy. These are ways that our groups can work together to try to better support this and ensure these costs are not astronomical.

"I think the challenges when we talk about rare diseases is there is a small population for each disorder and sometimes, we do not fully understand the prevalence of the disease. Encouraging a pharmaceutical company to actually work on drug development for particular diseases where they are not sure what the market will be is challenging."

Léon Van Wouwe:

The absence of clearly understanding the true prevalence of disease is one of the things that came about in the panel session as well as in the conference workshop that we did in Barcelona. That is something that people really struggle with. The other element when it comes to the business case for drug development is how can you commercialize on this? So what is the patient population size for real? Can you access them? The other thing missing is do we have a good understanding of the cost and burden of the disease for the patient as well as for society? This is definitely another frontier where we need to make a lot of progress, because I think the direct and indirect cost of people living with a rare disease is phenomenal. What we seldom see or take sufficiently into account is that for every patient, there is typically a family and a network of carers that are involved, and if you just simply do a back of an envelope calculation where you have a diagnostic odyssey of about seven years to come to diagnosis, that is seven years of a next of kin travelling back and forth to multiple specialists or first-line or second-line care before you actually can start doing something about the disease because you finally know what it is. That is a myriad of hours of lost productivity and going back and forth.

Karin Hoelzer:

I completely agree with everything that was said, but there are two additional areas where I think AI can really help eventually bring down the cost of cell and gene therapies. One of the big challenges with many of the cell and gene therapies is the very long follow-up, where FDA mandates at least 15 years of follow-up for clinical trials and in the post-market setting. So AI based models have a tremendous potential to bring down the cost of that. Then there are the cost of goods and the manufacturing capabilities, which are a big bottleneck for many cell and gene therapies. But

again, AI based systems can help with some of the standardization and some of the development of new strategies to bring down the cost. Finally, going back to the idea of the diagnostic odyssey and identifying patients earlier, many of the cell and gene therapies in the rare space that have been recently approved have a highly defined window because they are degenerative diseases. So you really have a very short period of time to identify the patient and administer the therapy. We are talking about the first year of life or the first four to five years of life. So using AI there to make sure that the patients actually can get to the point of receiving the cell and gene therapy by the time they age out of the eligibility period is really important.

Simon Alfano:
The other way in which AI can really help here, we talked about it before in terms of identifying clinical trial sites, is identifying sites where you may want to expand your cell and gene therapy site network to. Today, most cell and gene therapies are administered at a few hundred specialized centers. Fast forward 10 years, there will most likely be many more sites certified and able to administer those therapies while also being much closer to patients. It will be much easier in a way to also be able to access these therapies with a shorter travel time to monitor the disease. Also there will be less complexity for a doctor to administer those treatments and we will see next generations of cell and gene therapies that will hopefully be more accessible for patients as well.

"Today, most cell and gene therapies are administered at a few hundred specialized centers. Fast forward 10 years, there will most likely be many more sites certified and able to administer those therapies while also being much closer to patients."

Léon Van Wouwe:
To build on that, and to further your point, it is not just with cell and gene therapies, but it is in many therapies in rare diseases. Even if you understand the genetic basis or part of the disease, then we are still often left with the question, what can we expect? What will be the level of symptom penetration for this individual? So, another area where we believe that machine learning or AI can really help is in performing that patient characterization. It is predicting whether somebody is going to progress quickly or slowly. Because even if you have established that there is the genetic abnormality, do these patients actually need treatment now or are they going to need treatment in the future? Symptom penetration is often so diffuse. So that is another area where the focus is on for us.

Erika Berg (*host*):
Heidi, I was wondering if you could talk a bit about how individuals and families with rare disease can best participate to drive advances in the field. What can patients and families do to support these technological advances?

Heidi L. Rehm:
I think this is a really important question. I think a lot of individuals when they show up at their doctor's office assume that behind the scenes we are learning from all this data. In some cases we absolutely are. However, I think the patients and their families can be much more proactive in terms of enrollment in research studies and really ensuring that they are contributing their data in ways that it is broadly shared. Even being an advocate for whatever study or research program they are a part of, it is important to ensure those programs are actually sharing the data, beyond the walls, as with all the data breaches and security concerns there is a tendency to lock this data down to respect the privacy of individuals, which of course is really important. At the same time, every individual has a right to both contribute to and benefit from science. You have to balance that contribution and benefit that can be derived from sharing data with the privacy rights of every individual. I think each individual needs to really think about the benefits of sharing their data, participating in studies, and contributing clinical information in any way they can, because that is how we will learn about these diseases. We will be able to develop both diagnostics and treatments through all of that data being collected.

"You have to balance that contribution and benefit that can be derived from sharing data with the privacy rights of every individual."

Karin Hoelzer:
What I can say from our perspective is that we see patients being really generous with their time and with their data and wanting to help find a cure for themselves or oftentimes for those that come after them. However there is a flip side to it. Oftentimes we see that patients do not have access to their clinical data that is collected as part of a clinical trial, which is wrong on so many levels. We see that oftentimes groups that are collecting data on rare disease patients making monetary gains out of the data without that being shared with the patient groups that are engaged in collecting the data. Oftentimes there is the real or perceived limitation to having ownership over the data that is collected from the patients. Trust is a two-way street. Our patients contribute in clinical trials, they want to contribute data, and oftentimes it is their legacy, but there has to be a two-way street and a conversation. We see a lot of patient groups wanting to collect their own data and start up their own registry so that they are in the driver's seat.

"We see a lot of patient groups wanting to collect their own data and start up their own registry so that they are in the driver's seat."

Léon Van Wouwe:
In that case we are talking about the registries that collect the data of the patients that already know they are patients. The other big portion of the data that we need in order to leverage a lot of

the technologies that we are talking about here is just the typical general healthcare data. We see the same kind of issues and concerns in this domain. It revolves around who owns the data or who thinks they own the data. A lot of healthcare professionals are very protective of their data for very good reasons, but a lot of them also demonstrate a sense of ownership that is maybe misplaced, because it is ultimately the patient's data, whether diagnosed or undiagnosed. Talking about another frontier, an issue that makes things costly and difficult is the cost of access to data. That is definitely something that we are running into.

Karin Hoelzer:
To end on a positive note, we at NORD have been engaged for the last five years in FDA-sponsored projects to really share data on rare diseases, in particular control arms from clinical trials, etc. It is the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) program, and the idea behind it is that anybody who has rare disease data can share it. The data is hosted in an anonymized way with access controls, but it is a really great way for patient groups and pharmaceutical companies and others who have rare disease data to share that data and make it accessible. We have seen tremendous uptake among stakeholders, as well as some really interesting research projects where people were able to reanalyze data sets, combine data sets, and really found interesting new hypotheses and were able to make progress for their disease.

Erika Berg (*host*):
If someone was interested in making their data broadly accessible, how would they know how to share it?

Heidi L. Rehm:
The one site that some of my collaborators support is called MyGene2 and this is a website where a patient can actually upload their own genomic data, which allows them to share it as widely as they want to. That is one site if a patient actually gets their data, either from a clinical lab that they have had testing from or from a research program. They can upload that data, they can enter their phenotypes, they can put any information they want and can be in full control of sharing that data. That is one way, but individuals may be involved in other studies and they can inquire about how their data is being shared. They may learn that it is not being widely shared and then collectively, through patient advocacy groups really start to push, as Karin and Léon were talking about, to ensure that their data is more broadly shared. But that is one way that they can actively share their own data.

Erika Berg (*host*):
Thanks. So, I wanted to go around the panel for this question. Looking ahead, what do you foresee as the future directions or potential breakthroughs in technology-driven advancements in rare disease? What are you looking forward to? Where are you hoping that the field is going? Karin, can you start?

Karin Hoelzer:
Absolutely. Starting with patient finding, it is insane to me that oftentimes there are more trial sites than patients in a rare disease trial. That is highly inefficient. We know that AI and machine learning can really help there. I already talked about placebo arms and really making the best out of the data that exists so that trials can be run more efficiently and faster and in a way that is less cumbersome for our patients. Then there is leveraging of AI to identify more opportunities, such as repurposing drugs and better target leads, as well as cutting down on the diagnostic odyssey again. As AI is so good at pattern matching, so much better compared to humans, we see tremendous opportunity in improving the standard of care for all patients.

Simon Alfano:
I am very excited about the opportunities from technologies to really help innovate for patients with rare diseases. In particular, we talked about the big gap in rare diseases that are yet underdiagnosed and undertreated, so we need to really help find and understand the causes of all the diseases that are not yet fully understood or rudimentarily understood in terms of understanding the genetic cause, or if it is a non-genetic disease, the disease journey and drivers. Also, we need to really help find disease curing or disease modifying therapies for those patients. On the map of rare diseases, it would be great to close all those gaps of diseases that currently have no therapies available yet.

Heidi L. Rehm:
One of the areas that I am very excited about is some of the work we are doing within the Global Alliance for Genomics and Health, where we are connecting data sets around the world through federated approaches. Many countries cannot send data outside the boundaries of their country for legal reasons. I should mention it is costly to move data around in these large quantities that we have now, but we are setting up federated ways to query data, which means the data stays in its own site, but we send algorithms and analytical approaches around to all the data to learn from it. We are really just making the connections through all these sites around the world. I think that is going to allow much greater access than we have had to date, which I think is going to lead to really exciting progress for both the diagnosis of rare disease patients as well as identifying who is out there, where they are, and enable their entry into clinical trials and drug development.

Léon Van Wouwe:
We know from the work that we have been doing that it is possible to find those patients that are not yet diagnosed. We also know from the work that we are doing that it is possible to find them often significantly earlier than they tend to get diagnosed in clinical practice. So I am excited about that. I believe that it has the potential to actually change clinical guidelines, to an extent. Again, illustrating with an example, we have done work for one of our clients together on AATD, and we have learned a lot about the natural cause of the disease. We can predict patients at the moment, typically before they are also diagnosed with Chronic obstructive pulmonary disease (COPD). Now, if you look at the

guidelines for diagnosing AATD, it states that all patients with COPD should be tested for AATD. However, if you can find them and point at them before COPD is even coded for, then it is no longer a background disease against which you screen. It is actually a poor outcome of AATD, which is underlying. So that is why I think there is a potential to change clinical guidelines.

What I am personally most excited about, which is why I made the move from the drug development industry to Volv, is the impact I believe we can have on drug development. I think characterizing patients in all their diversity, de-risking clinical development, focusing on endpoints that are associated with early disease states, leveraging the technology to find potential biological markers that help you understand the biology, and matching it with what you know about mechanism of action is hugely exciting. I think that is where we are headed. I would love to come back for a future conversation about drug repurposing because that could take us another hour.

Erika Berg (*host*):

Many thanks to all of our panelists for being with us today. It has been a delight talking with you all. I learned so much and I hope our audience did as well. Thank you to Foundation Ipsen.

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