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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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Blooming against odds: Successfully navigating mental health in rare disease

Living with a rare disease can be an isolating experience, with impacts on both physical and mental well-being. Yet, the global community of those affected is vast, numbering over 400 million. This webinar aims to shed light on the unique challenges faced by individuals living with rare diseases and provide insights into evidence-based strategies for maintaining mental health resilience in the face of adversity.

The panelists include individuals with rare disease who have faced their own mental health struggles as well as scientists and policy experts who focus on mental health in the context of rare disease. Attendees will gain valuable knowledge on how the health care industry impacts patient mental health, ways to access mental health resources, and strategies for navigating the emotional and psychological aspects of living with a rare disease. The discussion aims to empower individuals with rare diseases to not only survive but thrive in their journey towards mental health and well-being.

Webinar attendees will:

- Understand the psychological impact of living with a rare disease
- Explore evidence-based coping mechanisms and resilience-building strategies
- Learn how to promote advocacy for mental health resources in rare disease and build community support

Panelists

Tanita Allen, B.A.
Advocate and author, Cleveland, OH

Kathleen Bogart , Ph.D.
Oregon State University, Corvallis, OR

Matt Bolz-Johnson, M.A.
EURORDIS, Paris, France

Juliet Lyons
Recording artist, Los Angeles, CA

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

The Conversation

Erika Berg (*host*):
For this first webinar, we are looking at an issue that impacts everyone: mental health. Living with a rare disease can be an isolating experience with impacts on both physical and mental wellbeing. Yet the global community of those affected is vast, numbering over 400 million. Today, we aim to shed light on the unique challenges faced by individuals living with rare diseases and provide insights into evidence-based strategies for maintaining mental health resilience in the face of adversity.

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

Tanita Allen:
Thank you for having me. I have Huntington's disease. Huntington's disease has been described as having Parkinson's, amyotrophic lateral sclerosis, and Alzheimer's all combined. It is a neurodegenerative disease and there is no cure at this time. I did not come from a family with this disease, so I was the first person to be diagnosed with Huntington's in my family. I was diagnosed in 2012, and I had many obstacles because of my journey of being diagnosed. I was told repeatedly that African American people do not get this disease and that was definitely a hurdle that I had to overcome.

Juliet Lyons:
Thank you for having me. I am really honored and excited to have an opportunity to talk about this and feel like I am heard. With rare diseases there is not a lot out there for us, so it is exciting to get to share. I am a recording artist, singer, songwriter, and composer. I was diagnosed with idiopathic subglottic stenosis, which is a mouthful, in 2019. It is a rare airway disease. It basically means the following: stenosis is narrowing, subglottic is just below the vocal cords, and idiopathic means there is no known cause for the growth of the scar tissue. It is an interesting disease because it is like a Groundhog Day situation. Day one starts when you have surgery to clear out the scar tissue and you wake up and you breathe like a normal person, and it is the best feeling in the world. Then, as is the nature of scar tissue, as time goes on the scar tissue starts growing back and breathing becomes more and more difficult, and you are due for another surgery. In my case, I am having two surgeries a year. It is a little different for everybody, but this has been my trajectory, and I am just working with it.

Kathleen Bogart:
Thank you so much for having me. It is so important to raise awareness about rare disease issues and to have these conversations with people who live these experiences. I was born with a rare disorder called Moebius syndrome that results in some facial paralysis and limited eye movement. As this

condition is congenital, it was my parents who went through the initial diagnostic odyssey, and it took a couple of years to find my correct diagnosis. During this time we got some false starts and misdiagnoses, and at one point my parents were even told that they should institutionalize me. My experience with rare disease growing up really made me fascinated with the experience of looking different, communicating differently, and having a rare disability. It led me to study disability and rare disease in my field of psychology. So, I am now a professor at Oregon State University in the School of Psychological Science and my research, teaching and advocacy work all center on rare disorders and disabilities. Today I will be sharing through both the lens of someone with lived experience and through the lens of someone who has worked with many populations with rare disorders.

Matt Bolz-Johnson:
Thank you very much for inviting me. I work at EURORDIS and I am the lead for mental health in our community. EURORDIS, if you do not know of the organization, is an alliance of patient organizations and we have over 1000 members in 74 countries. I have been at EURORDIS now for over 10 years. In working with the community, I have not met one person from the rare disease community who has said that this is not a big issue for them. So the fact that we are now able to put mental health into the spotlight, in order to take action, is a great place to be. I am thrilled to have the opportunity to talk about it today.

Erika Berg (*host*):
I think we have heard a couple times in our introductions, this concept of the diagnostic journey. So we are going to start from even before the diagnosis. Tanita, this first question will be for you. I know from your book, We Exist, that your diagnostic journey was full of twists and turns. Can you share with us a little bit about that journey and how it impacted your mental health?

> ***"I experienced a lot of depression, anxiety, and a lot of frustration with the medical community, after going from institution to institution and being told over and over again that there was no answer and that I basically had to live with this state of functioning. It was very difficult and I was stressed out all the time. I isolated myself from everyone as much as possible because I was embarrassed to be out in public. I was ashamed that I could not control my body and I could not get myself to stop shaking. So that was really a very dark period of my life."***

Tanita Allen
I did not come from a family with a history of this condition. So, for me, this was all new. It took about two years to get diagnosed. It all started with involuntary movements in my toes, which spread to my fingers, and then to my upper trunk and face, and my whole body was out of control. I would often go to the emergency room and was misdiagnosed as having a mental illness or misdiagnosed as being intoxicated or under the influence of drugs. I was also accused of being drug-seeking, as I was coming back frequently to hospitals for help. I had visited many institutions, with many different teams of doctors who were neurologists, movement disorder specialists and who were definitely very educated in the field of neurology. However, because I am African American that was a barrier to them diagnosing me properly or giving me the proper diagnostic testing needed to reach this conclusion sooner. Instead, I was told over and over again that Huntington's was the one condition that they knew for a fact that I did not have because of my race. I was told over and over again that it had to be something else, that it had to be mental, or that it stemmed from another issue. It was very frustrating for me. I went through a lot of depression and anxiety. I was afraid and there was a disconnect between my body and my mind, because my body had a mind of its own. The involuntary movements, which I know now to be choreic movements, were very hard to control before I was diagnosed. It was very embarrassing to be out in public and to be amongst strangers. People were afraid, people would get up and change their seats on the train, people would hold their kids closer to them in fear that I might be dangerous, and people would assume that I was under the influence of drugs. It was very hard for me. It was very scary because I have never been an alcoholic and I have never been on drugs. I was absolutely terrified that I would never find out the truth of whatever was going on with my body. I experienced a lot of depression, anxiety, and a lot of frustration with the medical community, after going from institution to institution and being told over and over again that there was no answer and that I basically had to live with this state of functioning. It was very difficult and I was stressed out all the time. I isolated myself from everyone as much as possible because I was embarrassed to be out in public. I was ashamed that I could not control my body and I could not get myself to stop shaking. So that was really a very dark period of my life.

Erika Berg (*host*):
Thank you so much for sharing that with us. Juliet, will you tell us a little bit about your journey?

Juliet Lyons:
Yes. I feel very fortunate that it was not like that. I do think that my case is a bit of a unicorn situation. The more and more I talk to people with rare disease, and particularly in my community, the more I hear that they have gone through awful situations. For me it started with having to cough and clear my throat all the time, and that went on for years without any other symptoms. I was not concerned about that particularly, but I started to get concerned when I noticed that I was getting winded easily and having to huff and puff and just feeing like I was really not getting enough air when I was exercising or on exertion. I started to talk to my inner circle, thinking it was kind of weird. I remember my sister saying, "Well, you are just out of shape." And I said, "Yes, but this seems a little extreme for that." It got worse, to the point where I would be gasping for air just going up the stairs. So I knew something was not right. I could also tell because when

I was anxious, I would have the same problem with not getting enough air. I could be anxious before that and not even realize it, because it is internal, but you do not realize how it affects your breathing until your breathing is compromised. At the time, I had preferred provider organization (PPO) insurance and I feel like that was what made the difference for me. Rather than experiencing what I hear from other people, with doctors saying, "Oh, you must have asthma, just get an inhaler," or "You have acid reflux," or "You just need to lose weight," I was able to refer myself to an Earn Nose and Throat doctor. On that very first visit with a laryngologist, he put a scope down my throat, and he could see what was happening. So I received the diagnosis immediately and that is traumatic enough just to say, "Okay, this is chronic and this is the rest of my life." My doctor said, "You are probably going to need to have surgery and we are not going to rush into it, but we will have that plan in place." That is exactly what needed to be done. So, that was a lot to process by itself and I can only imagine what it is like for people who go through years of not knowing and hearing things like, "Oh, you just need to lose weight." I see that so much in our community. People are dying, their throat is closing up, and sometimes it is to the point where an emergency tracheostomy is needed because no one is taking them seriously.

Erika Berg (*host*):

I feel like we have two extremes of the diagnostic journey here. Kathleen, I was wondering if you could speak to how common these stories are in regard to the mental health challenges during the pre-diagnostic stage, and what are the common psychological impacts of these varying journeys?

> ***"We also see that women and people of color are more likely to experience an extended diagnostic odyssey and experience this invalidation and accusations of drug-seeking and similar issues. This can result in healthcare trauma. It is hard to develop or rebuild trust with a healthcare team that has sent people astray, misdiagnosed people, or potentially given people treatments that are not helpful and, in fact, sometimes harmful. People can feel quite stigmatized."***

Kathleen Bogart:

Unfortunately, both are common. We hear Tanita's story and similar ones all too often. In fact, our research shows that people wait five to nine years on average to receive their diagnosis. That is a very long time to live with this uncertainty and invalidation. We also see that women and people of color are more likely to experience an extended diagnostic odyssey and experience this invalidation and accusations of drug-seeking and similar issues. This can result in healthcare trauma. It is hard to develop or rebuild trust with a healthcare team that has sent people astray, misdiagnosed people, or potentially given people treatments that are not helpful and, in fact, sometimes harmful. People can feel quite stigmatized. I really resonated with Tanita's story about being stigmatized on the train. I am also someone who has a visible rare disorder and because our conditions are not well known to the public, it can mean that there is a lot of misunderstanding and fear. That is a challenge that individuals with conditions that are sometimes visible experience.

There is a different kind of stigma that people with invisible conditions experience and that is significant invalidation. If the condition cannot be seen, doctors may say, "Oh, it is actually a psychiatric condition and it does not have a physical basis." People can also experience a lot of invalidation from those around them saying, "You don't look sick. Just buck up and figure it out." All of this means that people are often so relieved to get their diagnosis. This can actually be quite surprising for doctors, because sometimes the doctor might think this is a bad news diagnosis, but even with diagnoses that maybe have some emotionality attached to them; at least it is an answer. It is certainty. We find that once people receive their diagnosis, their mental health improves. I know that Matt will share the wonderful benefits of connecting with community once you get that diagnosis.

Erika Berg (*host*):

Thanks, Kathleen. Matt, after a diagnosis, how can people set themselves up for the post-diagnosis period and for good mental health in the long term?

> ***"[…] gender bias is real for a lot of rare conditions. Being a woman, it takes longer to get a diagnosis, because you are dismissed more readily. You are classified as being over-anxious or depressed. That is a big issue which is still really under-recognized in today's society and only now starting to get visibility."***

Matt Bolz-Johnson:

I just want to underline what Kathleen said, that gender bias is real for a lot of rare conditions. Being a woman, it takes longer to get a diagnosis, because you are dismissed more readily. You are classified as being over-anxious or depressed. That is a big issue which is still really under-recognized in today's society and only now starting to get visibility. I think that sense of always having to speak to clinicians, or even people in the community, such as family members or friends, and that low awareness of rare diseases really has an impact. It makes people feel very isolated, and it is frustrating having to constantly repeat what the condition is and how it affects you. In addition, no one really understands the implications or the severity, or whether it comes with invisible disabilities and what the risks are in the future. I think when you get a diagnosis, one thing which has the biggest impact, is actually being able to connect to a community of people with lived experience of the same condition. People that have walked that journey already. That sense of belonging is a game changer. Being in a room for the first time with other people with Huntington's disease is such a validating experience, because they know you and they understand your situation. That sense of community is, I think, the lifeline of the rare disease community.

Unfortunately, I think a lot of the time, the appreciation and recognition of how important that is, is overlooked. When someone gets a diagnosis for a rare condition, medical professionals should connect them to a patient group for that condition or direct them to an alliance like NORD, which is the National Organization for Rare Disorders, as they can direct you to the right group and community. When you are in these types of communities, the type of support which I need or Tanita needs could be very different. There is no one-size-fits-all. So being in a community, it gives you the opportunities to get some peer support on a one-to-one level or to connect in more social groups, whether that is a Facebook group or a private group. These groups are, as I said, a lifeline. When you are in these communities, they help you navigate the journey ahead. They give you trusted information, instead of doing Google searches and getting pictures showing the worst-case scenario, which can be terrifying. They settle a lot of fears in a very uncertain world, they give a level of clarity, and they make things more certain in terms of what is going on now and enable you to live in the moment. So, I believe these communities should be elevated more and recognized more, because I think they are the foundation of what we call psychosocial care.

"There is no one-size-fits-all. So being in a community, it gives you the opportunities to get some peer support on a one-to-one level or to connect in more social groups, whether that is a Facebook group or a private group."

Erika Berg (*host*):
Thank you. Kathleen, I am curious, have researchers investigated this at all to explore the benefits of these types of social groups, and is there one type of community that might be more advantageous than another? For example, is a Facebook group the same as meeting in person? Is there any guidance for those seeking a community, to help them decide what might be best?

"So, this is just speaking anecdotally, but I do think that there is some extra benefit to being in person surrounded by others who have had the same experience as you and perhaps look like you as well, if you have a visible condition. I think any way of getting support is certainly worthwhile."

Kathleen Bogart:
I love this question and I want to echo everything that Matt has said. I have seen the wonderful benefits of connecting with that peer support community. In fact, I did some research on the experiences of people with Moebius syndrome, which is the condition I have, who attend or did not attend a support meeting in person. First, to back up a little bit and as Matt was noting, many rare disease organizations offer support at some level. Sometimes it is online groups or Facebook groups. Sometimes organizations will have in-person meetings and it is common that they will occur maybe once a year or once every other year. Here in America, we are a big country, and often it is a big deal to travel across the country and to be in a space where for the first time you will meet others like you. Because our conditions are so rare that we would never encounter someone like us in our everyday communities. The Moebius Foundation does a conference like this, which is primarily focused on peer support and building community, and mixes in some expert information as well. In the study that we did, we used what is called a pre- post quasi-experimental design, and we examined people who did and did not attend the conference. We found a variety of benefits for those who did attend. That includes reduction in stigma, increased social support and increased knowledge. Now, I want to note that the two groups are not necessarily equal. The people who went to the conference maybe had some extra privilege and the ability to travel. Often these organizations will offer funding and things like that, which this organization does, but it does not cover everything. So, we were also interested in understanding barriers to accessing conferences like that. Financial barriers were one, of course, then there was the extra toll that travel can take on your body, and if you have a large family, uprooting that family to travel with you, and taking time off work, and all those things. So, there are a lot of different barriers that we can think of when we talk about different ways of accessing peer support. When people do experience those barriers, we think it is important to advocate for more funding to help people attend these in-person events when they want to attend them. However, that also speaks to the benefit of having a variety of approaches to offer support. For example, the support groups on Facebook will sometimes have Zoom meetings. Those are all great ways to get connected. To my knowledge, we have not directly compared the different modalities. So, this is just speaking anecdotally, but I do think that there is some extra benefit to being in person surrounded by others who have had the same experience as you and perhaps look like you as well, if you have a visible condition. I think any way of getting support is certainly worthwhile.

Erika Berg (*host*):
Thank you. Tanita, could you share your experiences with the Huntington's disease community? How do you engage with them and how have those experiences benefited you?

"I want to say that the Huntington's disease community is a beautiful community. We are small but we are mighty. Meeting people with Huntington's disease, or people that come from families with Huntington's disease, has been a game changer for me

Tanita Allen:
Well, first, I want to say that the Huntington's disease community is a beautiful community. We are small but we are mighty. Meeting people with Huntington's disease, or people that come from

families with Huntington's disease, has been a game changer for me. It is like having another family - my extended family of support. It is incredible going to the conferences, going to conventions, having Zoom meetings, or being part of Facebook groups or support groups. There is an organization that works directly with families called Help 4 HD and they have been amazing. They work directly with families, providing a wealth of information as far as places to go, how to get assistance or help in getting medications, as well as providing specific information about the latest research on Huntington's disease and health centers that are within their area. They can find out where to go to get treated and what specialists are needed. It has been amazing to connect with them and I am so grateful.

Erika Berg (*host*):
Do you mostly connect online or in person?

Tanita Allen:
I do both.

Erika Berg (*host*):
Juliet, do you want to tell us a little bit about your support networks?

Juliet Lyons:
Yes. I was just searching Google for "idiopathic subglottic stenosis" and finding all the scary answers, as Matt mentioned. I was not particularly looking for a support group, but some information from Living with Idiopathic Subglottic Stenosis, which is the support group that I belong to on Facebook, came up and I joined. It was one of the best things I could have done, because I suddenly did not feel so alone, and these people understand exactly what I am going through. I am not the most active person in the group, but just going on the page and reading people's stories and what they are going through at whatever point in this Groundhog Day thing is beneficial. They post things like, "It is a surgery day," or "I am really gasping today," and whatever it is, I get it. I have posted before too and people are there for me. I think another aspect that has been cool about it is we are comparing notes, and it is educational as well. For example, none of my doctors had suggested using a saline nebulizer, and that is information that is posted in the group and that is helpful for dealing with all the post-nasal drip stuff. So, we are getting tips from each other and we are sharing ideas, such as asking if anyone has tried acupuncture. We are all just trying to help each other live better.

Erika Berg (*host*):
That is wonderful. Matt, you said something before about building trust with the healthcare team and that it might be lost during the diagnostic journey. I would like to talk a little bit about the healthcare team as a part of that community. Tanita, maybe you could tell us how you engage with your healthcare team and what role that plays in your mental wellness?

"What is so great about my team is that we approach my health in a traditional way and a non-traditional way. So, for example, we look at diet and exercise, we focus on things like sleep hygiene, tracking my mood, journaling, and taking medication."

Tanita Allen
Well, my current healthcare team is the best that I have ever had throughout my journey. What is so great about my team is that we approach my health in a traditional way and a non-traditional way. So, for example, we look at diet and exercise, we focus on things like sleep hygiene, tracking my mood, journaling, and taking medication. I take medications every 12 hours but in addition to taking medications every 12 hours, I also implement other tools. I definitely seek therapy and peer support. I work with social workers and any other specialist that is sometimes needed, such as a physical therapist or a speech therapist. Sometimes there might be a need to try something new, like acupuncture, and I have tried that. There are so many different types of approaches with my care and these doctors are very open to widening the horizon because every person with Huntington's disease is different. You could put 10 people with Huntington's disease in a room and there are some similarities, but for the most part, we are all individually different. I like the approach that my team of doctors has taken and that is to treat the symptoms but also to look at my care in a holistic way.

Erika Berg (*host*):
You were in a situation where doctors were not believing you and not getting you where you needed to be. How did you go from there to finding this dream team of healthcare providers that seems like they are modern and proactive in terms of treating the whole patient?

Tanita Allen:
Once I got a definitive diagnosis through DNA testing, and that it was crystal clear that I had the genetic disease and that I was symptomatic and not just gene positive, I moved back to my hometown and I went to a Huntington's disease clinic, which is only for people with Huntington's disease. They have a comprehensive team of doctors that work together to handle your care and what makes it easy is that it is a clinic specifically for Huntington's disease. They understand the symptoms, they are very supportive, and they are very open to listening to me and having my feedback on any kind of medications that are prescribed, or maybe something that needs to be tweaked or some medication that needs to be eliminated. I bring in journals and we discuss my sleep patterns and my mood. They ask how my anxiety levels are and how I am in terms of depression. They take all of that into account and that is what I really like about this team of doctors. That is why, to me, they are the dream team.

Erika Berg (*host*):

Juliet, what is your experience with your healthcare team once you got that diagnosis? How did you find who you are working with now and how has that impacted your mental wellness around your condition?

Juliet Lyons:

Well, first, that sounds like a dream to have an idiopathic subglottic stenosis center. Only two people are diagnosed in a million, but it would be great to have something very specifically focused. An advantage for me is living in a big city like Los Angeles, where I have access to multiple doctors who could perform the surgery. My doctor is awesome. He is very sympathetic and empathetic. He always pats my shoulder and says, "I am sorry" every time he gives me a steroid injection because they are not fun. He is very open too, because it is a little bit of a Wild West, and they are still figuring out the best treatments for our situation. So if I say, "Can I try another steroid shot?" he says, "Yes, we will try it." So, it is cool to have somebody listening and I feel like he cares about me. And I think that it is important to have that connection with the person who does all the work on my trachea. He always tells the surgery team, "She is a professional singer, so be very careful when we intubate." I trust him and that is very important. On the side, I have a cognitive behavioral therapist that I have been working with for many years, and she is amazing too. I feel like having that focus on my mental health makes a big impact.

Erika Berg (*host*):

So glad to hear you have both found these people that are working for you and helping you out, but this experience may not be as common as we might want it to be. Matt, I was wondering if you would tell us about where healthcare providers are with respect to their awareness of the mental health issues related to a rare disease diagnosis, and any strategies that people with rare diseases could employ to find a dream team of their own?

Matt Bolz-Johnson:

We have surveyed our community and for most people, when they find the specialist or the dream medical team who knows about the condition, they feel very happy with the physical healthcare they receive. However, 85% of them report that their emotional and mental health needs are not being met. With rare diseases, you have a complex set of holistic needs. When you see a physician, it is important that it is not just the physical healthcare which is being addressed, but that there is some level of psychosocial support which is provided at the same time. One critical point in the rare disease journey is the point of diagnosis. When someone finally gets a diagnosis after five or six years of trying and seeing multiple specialists, how that diagnosis is delivered can either empower someone to face the challenge which they have been given or it destroys lives. Communication at that point of diagnosis is critical to really empower people to take on the challenge. What happens at that point, if it is done poorly, is that it can cast a long, dark shadow over all future healthcare interventions or contacts you have in the healthcare system in the future, because trust is eroded, and you never get that back.

"Psychologists like to tailor the care to the individual but if they do not know about the rare condition and they do not understand it, then it can be a barrier for them to feel like they can give the care or support which is needed. We actually call it "rare aware" care. There is training available, which is free online for any healthcare professional to take to learn about the commonalities of rare conditions. While each of the over 6,000 rare conditions are unique and diverse, there are a set of common characteristics, which if you understand those basics, you become rare aware"

In my opinion, we need to do two things. Medical care needs to be enhanced to be more psychologically informed. So that every time you speak to a nurse or a doctor, they consider the whole person in front of them and not just the patient. That they ensure the individual is listened to, but also heard, by checking in and asking, "Are you okay today? How are things going?" Understanding that point in the journey, the resources the individual must live with, and the treatment which is being given. What I mean by that is asking if there is a support network? Is there a family there or are they alone? It is about focusing on the needs of the individual at that point in time. It is called holistic care. It sounds quite simple, but most of the time that is not the case. If communication and those softer things are not done within the context of the medical care received, then the individual walks away really needing to see a mental healthcare practitioner and things are a lot worse. So, you can deal with these issues earlier and you can address things earlier and take preventive actions if holistic care is being given within the medical team directly. One of the aspects on the other side of the coin is when you connect with a psychologist. Psychologists like to tailor the care to the individual but if they do not know about the rare condition and they do not understand it, then it can be a barrier for them to feel like they can give the care or support which is needed. We actually call it "rare aware" care. There is training available, which is free online for any healthcare professional to take to learn about the commonalities of rare conditions. While each of the over 6,000 rare conditions are unique and diverse, there are a set of common characteristics, which if you understand those basics, you become rare aware. That goes a long way to enabling a psychologist to give the support which is needed. So, I think we need enhanced medical care to be psychologically informed and we need psychologists and mental health practitioners to receive rare aware training.

Erika Berg (*host*):

We have talked about community, and we have talked about the healthcare team and how important that is. I wanted to switch gears a little and talk about personal coping mechanisms. We are not always with our doctors or with our community. How do we cope and build resilience, day in, day out? Kathleen, I was wondering if you could talk a little

bit about what science has been telling us about the coping strategies that have shown benefits for people living with a rare disease?

"We know that, in America at least, the psychological training for our students does not routinely include information about rare disorders and, frankly, not much about disability or chronic illness at large either. This means that general psychologists may not be "rare aware""

Kathleen Bogart:
Many of the things that our speakers here today have talked about are useful, such as taking care of that sleep hygiene. One thing that my recent graduate student, Brooke Bryson, found is that people with rare disorders that involve fatigue can really benefit from activity pacing. Activity pacing is the idea that you are aware of the times of day when you have the most energy and the times you have the least. So, it means focusing on the things that you value and prioritizing them during the peak energy times, and then being sure to build in rests. This finding really aligns well with something that has come out of the chronic illness advocacy space, which is the idea of the spoon theory. The idea is that everyone wakes up each day with a certain number of spoons and some people have more spoons issued than others and it is your job to think about how to manage those spoons throughout the day. These things are helpful in ensuring that people can do the things that are most meaningful to them, while managing any fatigue or pain issues that they might have. I do also want to continue talking about what Matt was saying around psychotherapy. That is certainly a very helpful resource when someone's mental health issues rise to the level of that need. We know that, in America at least, the psychological training for our students does not routinely include information about rare disorders and, frankly, not much about disability or chronic illness at large either. This means that general psychologists may not be "rare aware" as Matt says, and I love that phrase. There are ways that they can seek out additional learning opportunities to learn more about it, but those that do are few and far between. So, one thing that we are really working towards is advocating for more built-in early training, because otherwise, it means that as you are assembling your dream team of healthcare professionals, there might be a whole new odyssey to find the right mental healthcare provider who gets it.

Erika Berg (*host*):
That is a challenge. Tanita, do you have any personal coping strategies that have helped you manage the anxiety that probably comes along with a rare disease and all the other complications?

"For me, I really work on my sleep hygiene. That is super important, because if I do not get enough rest, I am not able to function at a high level the next day or the following days. I keep a sleep journal and a health journal. I exercise between three to five times a week. It is just basic walking or chair yoga. I do guided meditation on YouTube, just simple five-to-10-minute sessions. I try to stay in the present. I try to not get too ahead of myself. I like to plan the next day's events the day before, so that I have a forecast of what is going to happen the next day"

Tanita Allen:
Yes, I do. For me, I really work on my sleep hygiene. That is super important, because if I do not get enough rest, I am not able to function at a high level the next day or the following days. I keep a sleep journal and a health journal. I exercise between three to five times a week. It is just basic walking or chair yoga. I do guided meditation on YouTube, just simple five-to-10-minute sessions. I try to stay in the present. I try to not get too ahead of myself. I like to plan the next day's events the day before, so that I have a forecast of what is going to happen the next day. So, from the morning I am going to be doing this or I have a doctor's appointment at this time. It helps with my anxiety levels, so that I do not feel disconnected with life, and I feel more connected. Those are some of the things that I do.

Erika Berg (*host*):
Thanks. What about you, Juliet?

"I like to do some yoga. I like to practice meditation. I like to spend time outside in the sunshine. It depends on how I am feeling as to how much physical activity I can do, but just getting outside and watering the plants or something similar is nourishing for my soul. I also try to live in the present and I also really try to practice gratitude, because there is always something to be thankful for."

Juliet Lyons:
There are a couple of similar coping mechanisms that I have. I like to do some yoga. I like to practice meditation. I like to spend time outside in the sunshine. It depends on how I am feeling as to how much physical activity I can do, but just getting outside and watering the plants or something similar is nourishing for my soul. I also try to live in the present and I also really try to practice gratitude, because there is always something to be thankful for. I am working on that. There was also a missing piece for me, which I just discovered recently, and it is the fact that I am a musician and I have this disease, and they have always been two different

and separate things. When I started exploring my feelings around my disease in my music, it was really therapeutic for me. It felt like expressing myself and my feelings around this experience through my music was what I needed to do. So that has been a cool thing for me too. I would say for people who paint or who like to horseback ride, if there is a way to mingle those two parts of your life together, I feel like it can be very beneficial, as it has been for me.

Erika Berg (*host*):
Tanita, you wrote a book. Did that activity impact how you were feeling?

> ***"Writing is very therapeutic for me. Documenting my journey was important to me."***

Tanita Allen:
Writing is very therapeutic for me. Documenting my journey was important to me. I wanted to basically document my back story. It started as just one chapter at a time and then it turned into a book. I am very grateful that I was able to do that and to express myself in that way. I also like to find other hobbies. I like to paint, I love art, and I love listening to music. These are the things that keep my mood even. It is important for me to do those things on a regular basis, and engage with things that I love, such as animals. I do not own an animal, but I love other people's animals. These are the things that bring me joy, the small things. That is what maintains my mental health and that is what keeps me healthy.

Juliet Lyons:
Yes! I would like to add that my two dogs are my biggest coping mechanism.

Erika Berg (*host*):
Matt and Kathleen, if you could comment briefly on access to mental health care. Where are we in the United States and globally? How challenging is it to access mental health services, and are there policy changes we could help advocate for to increase that access?

> ***"It does not mean that we are expecting mental health care providers to know about every single biological process of the thousands of rare diseases that we have. Instead, we want them to be aware of the many commonalities that we have shared today around experiences of invalidation and stigma."***

Kathleen Bogart:
Well, I can talk about the United States perspective, and I am excited to hear what Matt has to say about the situation in Europe. Anyone, regardless of their disability or disorder status, who has recently sought mental health care in America, may be aware that there are very long wait times and it can be hard to access care when you really need it. As I mentioned, we already have a situation where there are only a few psychologists and mental health providers who really have that training about rare diseases. Again, I want to emphasize what Matt said around being rare aware. It does not mean that we are expecting mental health care providers to know about every single biological process of the thousands of rare diseases that we have. Instead, we want them to be aware of the many commonalities that we have shared today around experiences of invalidation and stigma, and things like that. These will give them a leg up in terms of starting that therapeutic relationship. There are two things that we are working towards in the US with some advocacy groups. One is developing better training, which I have already talked about, and two is increasing the ability for trained therapists to practice across state borders. For example, in my field of psychology, there is something called PSYPACT (https://psypact.org/), where a certain number of states have agreed to allow therapists to practice across state borders. However, not all states are included. I have an ax to grind here because my state is not included. This means that you have your few expert mental health providers who could do a really great job of reaching out and connecting with people across the country and supporting them, but we are not able to license them in various states. There are also challenges around getting insurance payments across state borders. So those are some things that could really make a big difference in terms of access to care here in the US.

Erika Berg (*host*):
Matt?

> ***"The individual's mental wellbeing is impacted beyond the rare condition itself. We talked about social isolation and discrimination. There are things that we all can do in today's society to make people feel included in society and we can maintain flexibility, so that they can continue their education and employment despite having a rare condition. Those are the things that can improve the mental health of our community massively."***

Matt Bolz-Johnson:
Just a couple of things. Globally, the United Nations General Assembly recently approved a resolution for tackling the challenges of people living with a rare condition and their families. In this resolution the UN recognized people with a rare condition and the impact that has on mental health and wellbeing. The UN calls for member states to develop psychosocial programs for people with

a rare condition. So, that is a commitment from the UN and we need to see it be embedded at a national level. In terms of access to services, the foundational support of a community is the first thing which is needed, because that enables us to identify early any mental health issues and to implement preventive actions, which is far better than waiting later until they become more chronic. The psychosocial care, which is needed then is for medical care to be enhanced to be psychologically informed. We talked about rare aware mental health services. I just wanted to touch on this, but there is a wider issue that this is not all about the health system. Our mental health is affected by wider psychosocial risk factors. We have all experienced the recent pandemic and the impact that had on all of our lives with social distancing and the measures which were put in place. There are opposites of risk factors, which are psychosocial protection factors. The individual's mental wellbeing is impacted beyond the rare condition itself. We talked about social isolation and discrimination. There are things that we all can do in today's society to make people feel included in society and we can maintain flexibility, so that they can continue their education and employment despite having a rare condition. Those are the things that can improve the mental health of our community massively. Finally, the last point is that when you have good physical health, because you have the surgery for your throat or you get the support you need, this is a protection factor for your mental health and wellbeing as well. Getting the right physical healthcare is so important.

Standing out in the storm: Caregiving in rare disease

Whoever came up with the expression "Not all heroes wear capes" probably had a caregiver in mind. Caring for someone with a rare disease comes with a maelstrom of challenges, often requiring a multifaceted approach that addresses medical, emotional, and practical needs. This webinar aims to provide caregivers with valuable knowledge and strategies to navigate the complexities of caregiving in the context of rare diseases, empowering them to provide effective support while maintaining their own well-being.

The panel will bring together caregivers, scientists, and policy experts who will share insights and practical advice based on both research and personal victories. Attendees will gain a deeper understanding of the challenges faced by caregivers and learn practical strategies to enhance their caregiving skills and resilience.

In this webinar, participants will:

- Explore the unique challenges of caregiving in rare disease
- Learn practical caregiving strategies and how to access resources
- Hear about approaches that work to foster resilience and self-care among caregivers.

Panelists

Saundra Gumerove, Esq.
Attorney, Jericho, New York

Richard E. Poulin III
Teach RARE, Bangkok, Thailand

Danielle Rice, Ph.D.
McMaster University, Hamilton, Ontario

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

The Conversation

Erika Berg (*host*):
Caring for someone with a rare disease comes with many challenges, often requiring a multifaceted approach that addresses medical, emotional, and practical needs. In this discussion, we will tease out valuable knowledge and strategies to navigate the complexities of caregiving in the context of rare disease. Ultimately, the goal is to empower caregivers to provide effective support while maintaining their own well-being, which is not an easy balance. I would now like to welcome our panel.

Saundra Gumerove:
I am the parent of an adult daughter with Sturge-Weber syndrome, which is a rare disease that totally changed my life at her birth. I am now president of AHRC Nassau, which is an organization that provides services and support to people with developmental and intellectual disabilities, and I am a special needs lawyer. I work with individuals and families who have special needs. It is my way of giving back for the assistance that we received when Lauren was younger.

Danielle Rice:
I am a clinical and health psychologist at St. Joseph's Healthcare in Hamilton, an academic hospital in Ontario, Canada. I am also an assistant professor at McMaster University. I have been involved in conducting research about caregiving for several years now. I focus on rare disease caregivers, both broadly as well as for a specific rare disease called scleroderma. I also work with patients and caregivers that are involved in the rare disease community, by providing them with therapy and hopefully helping them navigate the challenges that can come with this experience.

Richard E. Poulin III:
I like to say that by day, I am a middle school principal. In the evening, my wife and I created a nonprofit called Teach RARE. We work on that during our evenings and our days off, and as educators we get the summer break too. There is a lot of work that we do with Teach RARE: working with parents, working with organizations in schools, and doing work with governments around the world to create awareness or to advocate for therapeutics to be approved and further research. Most importantly, we are the proud parents of a beautiful 6-year-old daughter called Rylae-Ann. She has an ultra rare disease called AADC deficiency and she keeps us busy as well.

Erika Berg (*host*):
Simply getting a diagnosis for a rare disease can be a winding and difficult journey, one that can take a toll on the caregiver. Richard, can you tell us about your diagnostic journey and how that impacted you and your family?

Broadcast Date: 18 July 2024 **Access this webinar here**

Richard E. Poulin III:
When my daughter was born, she was born completely healthy. There were no signs before her birth or just after her birth that anything was amiss. We were proud parents and were showing her off. We were traveling, because as international educators we live overseas and our family is located around the world. We made the trip to show off our newborn daughter and everything was great. We were getting settled into our new location in Singapore and about three months in, we began seeing some signs that were alarming. Initially, we had dismissed them as new parent jitters, thinking we were being overly cautious or just being worried parents. So we dismissed it for a little bit, but these symptoms, which started out as her eyes crossing and her limbs kind of tensing, were becoming more alarming. I initially attributed it to me as a father, because as she was missing some of her milestones, such as not grabbing out and not doing tummy time, I said to myself, "I am going to do some exercises with her and I am going to push her along."And I thought that I was just pushing her too much. However, they grew in severity and it looked like a seizure to us at that time and so we took her to the Emergency Room. The doctors there said, "You should have come to us sooner because this is a seizure and seizures can lead to brain damage or even death." After hearing that, I was a little disappointed with myself for not having acted sooner. We began with a diagnosis of epilepsy and they gave us medication and this medication left her literally like a sack of potatoes. It just did not feel right, and the diagnosis did not sit right with us.

So, we basically went through this hopping routine of visiting various doctors. Each time the doctors gave us a different diagnosis, such as cerebral palsy, while others did not know and said it was undiagnosed. We obviously wanted an answer. So we went through this process of putting our daughter through blood tests, EEGs, putting her in machines, doing genetic testing, and each time it came back as inconclusive or no results. One side of me is saying we have to push to get more tests, but the other side, as a parent, is saying that I do not want to subject my daughter to this, especially if in the end we have no answers. Later, I learned that not knowing or ruling out certain diseases or symptoms is part of that diagnostic journey. Despite this hopping around, no doctors actually gave us the answer. We were just very lucky that a Facebook post came up in my wife's brother's feed one day and he said, "This seems like what Rylae-Ann has." I went through the video and I saw the term AADC deficiency. Automatically, I began doing my research and from what I read, I knew at that moment that it was what she had. In going through these research papers, I found out about a clinical trial and the author of the paper. There was no indication if the drug was approved or if there were still clinical trials, all I knew was the author of these papers from years before. We had looked up the doctor's name and found out where he worked in Taiwan and were able to get an appointment with him.

"People may not be aware that the diagnostic journey for parents typically takes about four years. Many go much longer than that. Many never get a diagnosis. So we were fortunate to luckily figure out that our daughter had this rare disease, through our determination as parents to search for an answer."

A week later, on Christmas day in 2018, we flew to meet that doctor and obviously, the doctor and the team were completely surprised to see these people showing up saying that their daughter has this ultra rare disease. It affects around 130 people worldwide, since 1990. That number is changing because of improved diagnostic testing, but at that time they are just so surprised to see us there. What was very interesting was the doctor who has experience with this rare disease simply did a visual examination and listened to us, and through that appointment was able to very conclusively say, "Yes, I do believe she has AADC deficiency. We will do the test to confirm it." We were able to get a confirmation shortly thereafter. What sticks in my mind was that we did all these battery of tests and then here was this doctor who just did a visual examination and was able to confirm what we had learned through a Facebook post. It took a total of eight months from the time our daughter was born for us to get that diagnosis. People may not be aware that the diagnostic journey for parents typically takes about four years. Many go much longer than that. Many never get a diagnosis. So we were fortunate to luckily figure out that our daughter had this rare disease, through our determination as parents to search for an answer.

Erika Berg (*host*):
Saundra, what can you share about your experience?

Saundra Gumerove:
It was at the time of Lauren's birth that the doctors diagnosed her. The birthmark being on most of her face and above her eyes was an indication of Sturge-Weber syndrome. They kept us in the hospital for several extra days to do baseline testing, such as EEGs and EKGs. To this day, she still has a scar on her foot from the incision made to administer the anesthesia. They told us all the risks. My journey was a little different as I had difficulty asking if she was going to live. They did not give us any indication of whether or not her lifespan would be impacted. They said that Lauren could have seizures, she could have bilateral glaucoma, and she could have calcium deposits in her brain that would affect her future functioning. So for the first six months of her life, I basically stood over the crib watching. We were watching and waiting. Lauren had her first grand mal seizure at six months. At the same time, they discovered glaucoma. If anyone knows anything about glaucoma, your normal eye pressure is around 10 mm Hg. They discovered at six months that her eye pressures were 40 in both eyes and they needed to do emergency surgery. This all happened at once and thereafter, she had uncontrollable seizures for the first seven years of her life, despite being on medication. We had many bad experiences in hospitals. We luckily had a very good neurologist. The worst journey was with the glaucoma, because the world-renowned specialist at the time was located at Mount Sinai Hospital in Manhattan and he would put Lauren located at Mount Sinai Hospital in Manhattan and every three months, put her under anesthesia to do pressure testing of her eyes. That went on for seven years before he gave up. I will never forget it. He threw his hands up and said, "Well, there is nothing more I can do for her. I do not think there is anybody else in the world that can do anything for her, but here are the names of two doctors, one in Boston and one in California. Maybe they can help." He washed his hands of her

but it was the best thing that ever happened to us, because he only saw eyes. One thing we learn as parents of children with varying conditions is that different doctors see different parts of the body, but they do not see the person. We went to Dr. David Walton, who was one of the recommended people who taught at Harvard in Boston. He refused to put her under anesthesia. Jeff, my husband, would hold Lauren while he did the exams and he said, "Eventually, she will let me do it." That was true, but he never put her under anesthesia other than to perform surgery. He saw her as a child. If she was going to camp and she needed surgery, he would time everything so she could go to camp because it was important for her to have some happiness and non-medical time. He showed us that doctors can be compassionate and caring and see people. He was always very supportive of us as parents. So, my journey was a little different than Richard's but it took us years to be able to find medical care that could help her.

There is a Sturge-Weber Foundation and I did take Lauren as it was important for me that she sees that there were other people like her, because she never saw other people like her**.** Sturge-Weber usually only affects one side of the body and one side of the brain. We are lucky, as the birthmark covers both sides of her head and she has calcium deposits in both sides of her brain and the glaucoma is bilateral, so she is legally blind. However, I have to tell you, Lauren is the happiest person I have ever met. She has managed to find ways to address the way people treat her and she just allows it to flow right over her head. I look at her and think to myself, "I do not know where you came from." She still has issues and risks, most of which affect her eyes, as her seizures are under control. So my journey was a little different, but we still had that searching to do.

Erika Berg (*host*):

Danielle, we have heard two very different stories and journeys and I am sure every single caregiver out there has their own unique experience. In your research, what have you learned about the impact of getting a diagnosis on caregivers and their family, and is there a way to mitigate any negative impact of that diagnosis?

> ***"Often, when people are receiving a diagnosis for a rare disease, the caregivers actually experience a little bit of relief. That is not without the negative emotions that arise, such as worry, stress, feeling overwhelmed, and lots of concern, but there is often a sense of relief that these symptoms have been connected with a label."***

Danielle Rice:

Thank you Richard and Saundra for sharing that experience. Your experiences are, as was said, unique. However, some underlying themes are a little bit similar and align with the research for rare disease caregivers that suggest part of the role that caregivers end up taking on is the role of a scientist, the role of a care coordinator, and the role of an advocate. These are three large roles to take on while also parenting a child with an unknown condition and they are roles that people do not receive education for. That is a theme that I heard a little bit through both experiences and that really aligns with what research has shown as well. Often, when people are receiving a diagnosis for a rare disease, the caregivers actually experience a little bit of relief. That is not without the negative emotions that arise, such as worry, stress, feeling overwhelmed, and lots of concern, but there is often a sense of relief that these symptoms have been connected with a label. A little bit of validation comes when they can say, "I found it," or a doctor has found it, even after trying different routes to receive a diagnosis. The other part I will mention about what research shows is that this time of trying to determine a diagnosis is a really impactful and critical time for caregivers to those with a rare disease. In a fairly large study of caregivers to those with a rare disease called scleroderma, we asked caregivers, "If you could have any resource or any support system, regardless of money, what would you want?" We suggested things like free individual therapy, free group therapy, or someone coming to their house for respite care. We tried to put it all on the table. Caregivers replied that what they wanted was an online reputable source of information about their loved one's condition when they are newly diagnosed. I think that could certainly mitigate some of these challenges. However, I think it also speaks to the practical nature of some of what caregivers end up taking on. So yes, there are emotional challenges, but what they want is that information. At least that is what has been found in this research.

> ***"When you have a diagnosis at birth, it was clear from what the doctors were telling me that the likelihood of Lauren having a typical life was not going to happen. That pain is always there and always under the surface, but it is very hard to share with people who cannot really understand and who respond with, 'Oh my God, this is terrible!'"***

Saundra Gumerove:

That is a very interesting point. Having a child with a rare disease, or probably any disability, is very isolating. I am well-educated, I am a lawyer, I know how to work the system, and I know how to do research. However, I felt very alone and did not know where to turn, despite having good doctors. If I had found somewhere to talk to people or not feel so isolated, I think that would have helped. I also think that we, as parents, want the best for our children, but we also go through a period of grieving. Particularly as Lauren was my first child. You have all of these hopes and dreams somewhere in your brain of what that is going to be like. When you have a diagnosis at birth, it was clear from what the doctors were telling me that the likelihood of Lauren having a typical life was not going to happen. That pain is always there and always under the surface, but it is very hard to share with people who cannot really understand and who respond with, "Oh my God, this is terrible!" I was also told from an early age that there were places for children like Lauren, and I did not have to live with it. My reaction to that was, "You are not taking my child away from me."

Erika Berg (*host*):
Richard, I was hoping that you could tell us about how you created this amazing resource for caregivers called Teach RARE. Can you share how you have been helping caregivers get healthcare in parts of the globe where it is particularly challenging?

Richard E. Poulin III:
What initially prompted us to get into this was, as Saundra talked about, this period of grief. We could have a whole session on this process that parents go through. There are a lot of differences, but there a lot of similarities as well. Once I accepted my daughter, I was still just a wallflower. I was just listening in, getting resources, and dedicating myself to my daughter, obviously. Then one day I was on an online webinar and there was another parent whose son had passed away from AADC deficiency, which is very common in our community. Life expectancy is around 4 years old. Here he was, and his son had already passed away. He had no tie necessarily to the community anymore. He could easily just have gone on with his life, but he was still giving back to the community by trying to raise support, give motivation to parents, and share his story. I just thought to myself, "Who am I? I am just sitting back here doing nothing, while here is this father giving his all." It really caused me to change my mindset. I write a weekly column for AADC News and I talk about this journey of how you are changing that mindset that Saundra was talking about. You have these dreams, and obviously the dreams change. For me it was like I was pushing through and was trying to make these dreams of a typical parent happen, like going to Disney World, and then you end up doing more harm and you do not create memories and your child is definitely not enjoying it.

> ***"We have created some curriculum, lesson plans, and children's books. This makes students more aware of rare diseases, but also inspires them to be future researchers, doctors, change-makers, and problem-solvers. Our organization is also working with the schools and organizations to make a broader impact, and it has just been so fulfilling for us."***

So, by going through this process, my wife and I came through to the other side and we wanted to give back to our community. We started Teach RARE because I am a principal and have a background in language development and special education and my wife is a special education teacher certified in autism and many other disabilities. We knew we had all these resources and all these networks and we just wanted to leverage all that and be able to give that back. Although we are based in the U.S., we are very international and work with international schools so we can expand this outreach to other parents around the world. We provide services, usually it is one-on-one and face-to-face or it can be online. We provide them with tips as they are the front line of caregiving, in addition to being the healthcare coordinator. We are giving them strategies on how they can coordinate appointments with doctors, physical therapists, and speech therapists, because those separate organizations do not talk to each other. You do not have this treatment plan that each of those healthcare professionals can rely on, so we give that information to the parents. As rare diseases are rare, we are spread around the world, so we organize events to bring people together. As we still wanted further reach, we began leveraging the organizations and the schools that we work with to do more about training teachers and building inclusion in the schools. We have created some curriculum, lesson plans, and children's books. This makes students more aware of rare diseases, but also inspires them to be future researchers, doctors, change-makers, and problem-solvers. Our organization is also working with the schools and organizations to make a broader impact, and it has just been so fulfilling for us. I think when you go through that process of acceptance that Saundra was talking about, that many rare disease parents go through, and you then actually become involved in your community, you begin to see more meaningful memories happening in your family. More results for us were happening because we were collaborating with more people. You can do things on your own, but when you collaborate more happens. Not only were we making meaningful memories, but our daughter was benefiting from those collaborations as well by making some progress or by having a more meaningful life.

Erika Berg (*host*):
That is incredible. Saundra, I know you are doing some incredible things too. Can you tell us about them?

> ***"I wanted to give back to my general community because I knew that there were other parents and families who had no idea what to do. They did not know that they could get services and supports from zero to 5 years old, and then special education services and adult services. The system anywhere in the U.S. is not easy and it is not simple."***

Saundra Gumerove:
Lauren's father left when she was six months old, and I was a single parent until she was 7. When I remarried my husband Jeff, who is a wonderful human being, he adopted Lauren. I said to him that I wanted to be at home with my kids. We decided to have another child and I was general counsel to a commercial finance company, so I was on that US corporate ladder. I quit my job and I decided to open a law practice and I wanted my law practice to be limited to people with special needs. As I said, I am fairly educated and I know how to work the system, and it was hard for me. As a single parent and as a mother of a child with disabilities, I knew nothing when she was born. Having learned what I had learned over the years and luckily having found someone who approached me and was able to tell me about the schools where Lauren could go and about special education and the services and supports we could get, I decided that I wanted to give back. I also got very involved with AHRC Nassau and I believe they saved her life. Lauren had been expelled at age 6 from a special education school on Long Island, and they wanted me to put

her in a residential placement, which happened for maybe a year, and then I found AHRC through a friend of Jeff's family. Within six months of Lauren going to their school, the behaviors that had gotten her expelled were gone. I do not know what they put in the water. I do not know what they do in that school, but they enabled me to keep my family together and they enabled her to grow and to thrive. I think it was the level of acceptance. Nobody made fun of her as it was not acceptable at that school. The teachers knew how to deal with children with bizarre behaviors. Lauren had previously had all of those awful life experiences. She was in and out of hospitals, her father left and I just wanted to say, "Can't you understand? You are supposed to be able to deal with children." So I decided to get very involved with AHRC Nassau and I became a member of the board. I am now president but I would do anything for them because they enabled us to have a life.

I wanted to give back to my general community because I knew that there were other parents and families who had no idea what to do. They did not know that they could get services and supports from zero to 5 years old, and then special education services and adult services. The system anywhere in the U.S. is not easy and it is not simple. So I opened my practice. I did speak with the then executive director at AHRC and I said, "Do you think that I can make a living?" It was something I wanted to do, but I had to make a living and help support my family. He thought that I could and I did. If it was not for Lauren, I would not be sitting here. I would not be doing what I am doing. I have this wonderful, amazing child who has two amazing siblings, and who has taught us about how to navigate the world even when you are different.

Erika Berg (*host*):

Thank you for sharing that. We have heard that finding the right health care is a challenge when you are a caregiver of someone with a rare disease. Finding legal support can also be a challenge. I want to switch gears a little and talk about the mental health aspect of caregiving. Danielle, since mental health is a big part of your research, I am wondering if you could share some strategies for how to address mental health issues in caregiving for the caregivers themselves. With all of the many things that they are looking out for, how do they take care of their own emotional needs?

> ***"There are positives that can be integrated in someone's life when supporting a loved one with a rare disease […] There are a couple of tried and true support strategies that can help mental health in this realm. One is certainly, as already mentioned, trying to connect with a rare disease organization."***

Danielle Rice:

As we have discussed today, the challenges that come with caregiving for someone with a rare disease can include diagnosable conditions like anxiety and depression, but also feelings of caregiver burnout, overwhelm and stress, as well as financial challenges. At the same time, Saundra just gave such a beautiful statement about some of the positives that can happen while you are in this role that you did not choose and which was unexpected. It can bring closeness in families. It can push someone to change their career or become experts in advocacy, and I think that some of those benefits are sometimes forgotten. There are positives that can be integrated in someone's life when supporting a loved one with a rare disease. I just wanted to mention that before I get into some of the more negative aspects, which are sometimes the mental health challenges that can accompany rare diseases.

> ***"Self-compassion is that internal dialogue that is saying, "I am going to make mistakes just as everyone else does. That does not make me any less of a parent, a caregiver, or a loved one." It is really trying to change that self-critical voice that often we all have, but that can be amplified when trying to navigate a really challenging system, and trying to make it a little more soft and compassionate by bringing the same voice we would say to a best friend to ourselves."***

There are a couple of tried and true support strategies that can help mental health in this realm. One is certainly, as already mentioned, trying to connect with a rare disease organization. That can be a local one, if there are enough with the rare disease, or it can be more broad and international, as Richard spoke to, looking for anyone with a rare disease more generally. Those types of support systems are hugely beneficial. It has been shown that peer support groups are beneficial as well for caregivers as they can be a great way to connect with others for emotional and practical support.

Furthermore, there are a couple of strategies that are quite common to help the mental health of caregivers. One of them is something called behavioral activation, which is just a fancy way of saying trying to take time for yourself, which is often one of the biggest challenges. We can break this up into small, medium, and large ticket items. A small behavioral activation item could be something like: can you sit on the porch and drink a cup of coffee, during a nap time perhaps? Could we then work up to going to a coffee shop for 15 minutes and then returning home? This can go all the way to a large ticket item, such as going to grab lunch with a friend for an hour. This type of focus on you, the caregiver, is needed to fill the cup up, but it has to be tailored to what is feasible when supporting a loved one with a rare disease. Of course, this is going to be different based on everyone's situation. However, trying to write out your small, medium, and large ticket items and trying to plan a few, even once a week, can be hugely beneficial. The second approach that has some really good research support behind it is self-compassion. This is also a name that does not need to be as fancy as it is. It is the idea of trying to be kind to ourselves. I do not want to put Richard on the spot, but he shared something that a lot of caregivers will share, which is that there is some self-blame or asking, "Is there a way I could have done something differently to change the outcome

of my loved one's experience?" Self-compassion is that internal dialogue that is saying, "I am going to make mistakes just as everyone else does. That does not make me any less of a parent, a caregiver, or a loved one." It is really trying to change that self-critical voice that often we all have, but that can be amplified when trying to navigate a really challenging system, and trying to make it a little more soft and compassionate by bringing the same voice we would say to a best friend to ourselves. If my best friend came to me and said, "Hey, I think I am a terrible parent because my child got diagnosed with this disease". What would I say to them? And can I bring that same voice to myself? Those are just a couple of somewhat feasible things to try and implement, where possible, to address some of those mental health challenges that can come up.

Erika Berg (*host*):

Richard, would you mind sharing with us how the caregiving experience has affected your own sense of well-being, and if you have had any successes or personal strategies that have worked for you in helping yourself with mental health?

> ***"When you stop trying to take on too much and when you step away from trying to have this mentality of, "I am going to give 110%", then you actually end up doing more for your family. You have a more meaningful journey together. We were able to provide better care for our daughter because we were not burned out. We were not stressed. I had a lot more patience with my daughter and I had a lot more energy. So I think for us, just giving ourselves that time really made a huge impact on our life."***

Richard E. Poulin III:

In the beginning, when we were going through this process and were trying to get a diagnosis, we shut off all communication with friends. We went from posting all these photos of our newborn baby to just cutting off social media and cutting off our ties with our friends. We did not go out. If we did go out, it was just the three of us. So we were very isolated by choice, but we were going through this process. What we did not realize is that we were burning ourselves out, as Danielle had said. There is obviously this grief, this disappointment, and all the other emotions that you go through. We did not even realize that we were going through depression. It kind of caught us off guard. Luckily, I had my wife, Judy, with me. We just put both of ourselves in check and said, "Hey! We need to take a more systematic approach to this." What we did is exactly what Danielle was saying, we gave time to ourselves and for me it was with high intensity workouts. A high intensity workout is basically focused on 30 to 45 minutes of getting your exercise in and getting back. I wanted to make sure I had my exercise to burn off my stress, but I did not want it to consume too much time. I cannot go out and play golf anymore; it is just not feasible and does not work into our schedule. Making that slight change really worked for me and then I made sure that I gave that time to my wife so she had her time. My wife likes doing massages and pampering herself, with facial massages and things like that. They are simple things, but you come back rejuvenated and fresh and you feel more motivated. During those times where she is just sitting and relaxing, she is coming up with more ideas and she returns home full of great ideas. So for us, it was doing what worked with our schedules and making sure that it was something that was aligned with what we were doing before the diagnosis that still made us happy, in a slightly different way. Really quickly, things changed for us. When you stop trying to take on too much and when you step away from trying to have this mentality of, "I am going to give 110%", then you actually end up doing more for your family. You have a more meaningful journey together. We were able to provide better care for our daughter because we were not burned out. We were not stressed. I had a lot more patience with my daughter and I had a lot more energy. So I think for us, just giving ourselves that time really made a huge impact on our life.

Erika Berg:

Saundra, same question for you.

> ***"I had a doctor once say to me, "You have to take care of yourself because you cannot take care of her if you are not in a good place." It took me a long time to really internalize that and make that happen."***

Saundra Gumerove:

Well, I was a single parent who had to work to support us, and I was burning out. I could not imagine when Lauren was little that anyone could take care of her as well as I could, when I could. There was also the guilt of working eight or 10 hours a day and leaving her with caregivers. When she started school, it was a little easier, but I actually had a panic attack when I was driving with her in the car when she was two and a half. I remember thinking, "I do not know how we can survive." I was on the elevated Brooklyn-Queens Expressway in Brooklyn, New York. I was trying to figure out how I could have a car accident that would kill us both because it was unacceptable for me to die and her to live. It was unacceptable for her to die and me to live. I could not figure it out, so I did not do anything. Thank goodness I was in therapy at the time and I called my therapist and he said, "You had a panic attack." So we started, through therapy and through group therapy, to address those issues because it is overwhelming, particularly when you are still trying to figure it out and find a school or find appropriate doctors. Also, many families where there are children with rare diseases and other disabilities are divorced or are families where one parent or the other has left. I went through that. Being a single parent is hard enough when you have a typical child, but with all this extra stress, it was very hard. Again, for me, working and finding a way to give back really helped. I had a friend who was one of Lauren's teachers when she was three, who showed the world she was educable. Up until then, nobody thought she could be educated or that she would ever speak or ever get past the behaviors. She showed me that there was hope for Lauren, which helped a lot. I think

for me it was work, having a distraction and finding other people that I could work with and through. I did everything I could for Lauren. You said something that struck me and that is, "It is hard to find time". I had a doctor once say to me, "You have to take care of yourself because you cannot take care of her if you are not in a good place." It took me a long time to really internalize that and make that happen. Having other people who were going through the same thing, and it did not have to be someone who had a family member with Sturge-Weber but someone just going through something similar to me, was very helpful because I could see that there was light at the end of the tunnel. But it was hard.

Erika Berg (*host*):

Richard, in what way, through Teach RARE, are you working toward addressing the mental health needs of the population you serve with that program?

Richard E. Poulin III:

It has been fun because it has been therapy for us as well, by just being able to communicate and collaborate with all the parents that we are reaching out to. One of the best things that we have done is these events where we bring together parents of the special needs and rare disease communities. We invite them to an event and they go through stations. They are able to meet with healthcare professionals, physical therapists, occupational therapists, speech therapists, and other types of therapists. They are learning and they are taking strategies home with them, but more importantly, they are there with each other to just share stories and to lean on each other. Also, during the events, my wife will take all the moms out to do a massage, so there is a timeout where we will have a masseuse at the event. This means that the moms are able to take some time away, get a massage, and they are all talking with each other. We had that happen at our last event in Bangkok. At an event in Boston, we took all the parents out to eat. We had this army of strollers and wheelchairs going through the cobblestone streets of Boston. We went out to get some lobster and to the aquarium, and we were all there together helping each other out, because you may feel unmotivated or feel like you cannot do it if you are by yourself. However, when you have a group of people who all have the same challenges and know how to adapt to a curb when crossing the street for example, we are able to help each parent. You coordinate this type of activity together, and you are able to make these memories together. By making sure that we embed these types of extracurricular activities for parents into our events, either with alone time or going out as a group, we have been able to add these memorable experiences that have filled up our photo roll when we look back at each of our events.

Erika Berg (*host*):

We have brought up a couple times this notion of burnout and how it is a big issue in caregiving. Danielle, are there any practical tips or strategies for avoiding burnout for caregivers? Has research shed any light on this?

"You might think, "How would I have time to go for lunch with a friend? Why would that be a priority in my life?" Shifting that to the perspective of, "This will help me with my health and well-being, which in turn helps my loved one," is one way to reframe your thoughts in order to accept that one's health is important."

Danielle Rice:

Yes, and it is quite similar to the behavioral activation and self-compassion tips we mentioned previously. Number one is certainly trying to work on accepting that your health is important and that your mental health requires some space and some time. It is a really hard thing to try and accept and build time for when, again, schedules are filled with appointments caring for your loved one, researching, and doing advocacy work on top of work. It is incredibly challenging, but even having that mindset of accepting that you will not be able to continue at this rate long-term, is a really relevant and important first step. Sometimes, a way to sort of try and work towards that acceptance is with the rationale that to be able to care for my loved one, I need to be at some sort of baseline level of health and mental health. That can help drive that acceptance piece. The other aspect that sometimes people hold onto is knowing that a caregiver's health is actually directly related to their loved one's health. So if you want your loved one to be as well as they can be and attend their appointments, one of the things that is correlated with that is the caregiver's health. You might think, "How would I have time to go for lunch with a friend? Why would that be a priority in my life?" Shifting that to the perspective of, "This will help me with my health and well-being, which in turn helps my loved one," is one way to reframe your thoughts in order to accept that one's health is important. The last thing I will say on that piece is just breaking down the expectations into way smaller ones. The examples of the high intensity workouts are fantastic. However, if someone is starting without working out at all, can you simply have the goal of putting on running shoes and going for a five minute walk? If you are starting at no exercise, and are really grading that at the smallest step, you would look at me and say, "That is silly and way too easy." But that is the step I would want someone to start at. Then they can work their way up to 40 or 45 minute high intensity workouts. It is really about breaking that down once you have accepted, "Okay, I need to focus on my health. Where do I start?" Start at that smallest step. We want to set caregivers up for success. So those would be a couple of tips that research has really found relevant. Again, those help both the caregiver's and the loved one's health and well-being.

Saundra Gumerove:

The one thing you have not mentioned that I think helped me was realizing that Lauren was entitled to a life, that she was probably going to outlive us and that she would be able to achieve some level of independence. What happened in my world is AHRC has a sleepaway camp, where Lauren happens to be right now and has been going for around 30 years. They had a one week session and I knew and trusted the people who were running the camp and they encouraged me to let her go. I will admit that I

would wake up at three in the morning and I would call the camp going, "Is she okay?" And they would say, "Hold on, we will go run down to her bunk." They would run down and come back and they would say, "She is sleeping, she is fine." I came to realize that if she were in a safe place for a few days and I could sleep for a few days with minimal interruptions, then for the other 51 weeks of the year, I could deal with anything. Finally, that grew and Lauren ended up going to camp for eight weeks because she loved it. The camp would say to me, "What would you like her to learn this year?" I remember one of the first things I wanted her to learn was how to wash her hair in the shower so that I did not have to shower with her to wash her hair. They also tried to teach her to tie shoe laces. That was not successful, but as today we have Velcro, it does not matter. However, recognizing that she is entitled to a life too was really hard for me, but once I got there, it made a huge difference in her ability to be independent and have good self-esteem. I do not know if that has entered into your research, Danielle.

Danielle Rice:
Yes, you are right about respite care. I think the way that you have worded it ("making sure she has a life") is not probably well described in any quantitative papers, but what you are saying comes through in a lot of the interviews, absolutely. I think one of the biggest challenges with that type of experience is accessibility. So the fact that you have access, and you know the organizations that support those types of experiences is phenomenal. I hope that those can be expanded. At least in Ontario, they are pretty few and far between, so I think it is a really good area that probably needs some more resources, as this whole area does.

Erika Berg (*host*):
I was wondering if we could talk about the role of community and networks of people. Is there research supporting the role of community in networks for caregivers? For people who are feeling alone and isolated, how can they find a network that will be supportive for them, whether that is for their family or other caregivers?

Saundra Gumerove:
I know that today our community and many of the communities I am aware of across the U.S. and some internationally are online. So we have resources today that did not exist when Lauren was born. Lauren was born in 1981 and the internet did not exist. Social media did not exist. Today, there are things available; you just need to do a little research as to whether or not they are legitimate organizations.

Danielle Rice:
I think looking online is great and this could also be a good question to ask your specialist. Not all of them will know the answer, but some of them are really well-connected with specific rare disease organizations, or at least have a starting point of where to go. With scleroderma, for example, which I work closely with, we have a lot of rheumatologists that are directly connected to the organization to try and disseminate and share some of these options for the support network. This is because the rheumatologist will, unfortunately, only have maybe 20 minutes with patients and their loved ones. However, that community organization is ready to spend as much time as needed and they develop these patient-led education nights and support services and conferences. Asking your health specialist can sometimes be a good lead if you are finding it difficult to figure out what is reputable or to find that connection.

Erika Berg (*host*):
Richard, I know you are building this community yourself, but what role has community played in your life and what advice would you give to others who are looking to find a community?

Richard E. Poulin III:
I think it is important to just go back to what was said earlier by Saundra and Danielle, that we are the coordinators of healthcare. I remember at the last rare disease day event, on February 29th of this year, they shared a survey out of the UK, which showed that more than 70% of the parents were the coordinators of the healthcare. This means they are the person who was finding the doctor, finding the physical therapist, and finding all these places. So I think it is important to say that this is going to probably be a part of the journey for many of the parents. Be prepared that you are going to be reaching out to different healthcare providers and do not get discouraged. I know that Saundra had that story and I had that similar story where my daughter was denied services because they did not want to take on the case or they, for whatever reason, did not want her to be a part of it. So be prepared that you are going to be this healthcare coordinator and approach these different places.

Because our daughter has this ultra rare disease, of about 130 people, the pool of parents that we can reach out to is even smaller and the organization itself is small. However, you can reach out to other organizations that have similar symptoms. So for us, we connected with cerebral palsy and epilepsy groups and they are much larger. They have great funding and they accepted us with open arms. Just because you do not fit the label, if you find another group that is nearby that has similar symptoms or just another group where parents are going through similar challenges, I think you should definitely reach out to them and find out what resources are available and continue reaching out to different organizations. You do not have to stay with one organization because it is the first one you found. There are plenty of organizations out there and, just as Saundra has said, many of them are online and many of them are offering free resources, such as Teach RARE. Being able to find that community that you can access allows you to start creating this network which grows from there. Again, from our personal journey, once we started doing that, I found so many organizations and groups that I never knew existed. It is great to be a part of that community once you get yourself involved and become an active participant.

Saundra Gumerove:
If I may add, organizations and various communities and schools have different philosophies and personalities. If the first one you

find does not fit you, look for another one. I say this to people all the time. AHRC Nassau worked for my family and it worked for me. On Long Island, we have lots of organizations, so there is a lot of choice, but it did not work for all my clients. I think you need to find a place where you are comfortable and your child or loved one is comfortable, but do not give up because they are out there. They are there and you just have to find the one that fits you, because it goes both ways.

Erika Berg (*host*):

I wanted to ask you, Saundra, if you had some advice for caregivers in terms of long-term planning for the future of their loved ones? I imagine this might come up in your business.

> ***"So we need to ask ourselves, "Will my loved one be able to live alone?" If the answer is no, then where are they going to live? […]***
>
> ***I encourage people to think about the future, which is one of the hardest things for us to do, and to plan for that future. No matter where you are, there are always things that you can do."***

Saundra Gumerove:

In my practice and in my life, it comes up all the time. I think we need to think about what is going to happen, as a family, when you get to the point where you can address these issues. In the beginning, we are all just putting one foot in front of the other and we are just trying to make it through every day. However, when you can, you need to think about what your loved one, be it your child, sibling or another person, is going to need. In the U.S., we talk about estate planning and wills. In the U.S., we have financial supports from the government: Social Security, Supplemental Security Income, and Medicaid, which are needs-based or financially-based. There is planning you can do to ensure that your child gets what they need from the government. Now, some people will say to me, "Well, I do not know if I want government benefits," but in some states, New York being one of them, you cannot access services unless you have Medicaid benefits. I do not know why, but that is a fact. So you plan for what you can, and find out what is available for your child because they are still going to need the services. Many people with rare diseases will need some type of therapy throughout their life. Therefore you want to plan for the availability of those services when you are no longer there. I also say to families to look for the organizations that are available and find the one that works for you that can provide the support needed when you are not around. It is really hard to think that far in advance, particularly if you have a younger person, but I think it is important to have an estate planner and an idea of where you want your resources to go. We all lived through COVID and people died who never expected to die at the age that they did. So we need to ask ourselves, "Will my loved one be able to live alone?" If the answer is no, then where are they going to live? For me, siblings were not the answer. My three daughters are all very close. Lauren speaks to them frequently. However, I never wanted Lauren to live with them because I know the impact that her living with them could have on their futures and their lives. I do not ever want be a burden on them and I do not want her to be a burden on them. So we have tried to encourage her independence, although she will never be alone, but ensure that we have her in a place where we know she will be safe. Those are the kinds of things I talk to families about. I will turn to someone and say, "So when is your child moving into a group home?" and they will look at me like I am crazy. As much as we would all like to outlive our loved one, for most of us that is not the reality. Therefore, I encourage people to think about the future, which is one of the hardest things for us to do, and to plan for that future. No matter where you are, there are always things that you can do.

Keys to success: Unlocking health care access for rare disease

Health care access is a global challenge, compounded for rare diseases in which diagnostic and treatment options may be both geographically and financially out of reach for many patients. Yet access is attainable, and in this panel discussion we will explore strategies for overcoming obstacles to access by hearing from those who have successfully done so, as well as from experts in the fields of bioethics, biomedicine, and policy.

Our panelists will share their insights, experiences, and best practices in navigating the complexities of health care systems to ensure equitable access for rare disease patients. We'll also hear from people who have navigated the health care access landscape, and learn from their success stories.

In this Science webinar, attendees will:

- Gain a deeper understanding of the unique challenges faced by individuals with rare diseases in accessing health care worldwide
- Learn about successful advocacy initiatives and strategies employed to overcome barriers to health care access for rare disease patients
- Acquire insights into the role of policy reform and innovative solutions in improving health care access for individuals with rare diseases.

Panelists

Jeromie Ballreich, Ph.D.
Johns Hopkins University, Baltimore, MD

Elizabeth Currid-Halkett, Ph.D.
University of Southern California Los Angeles, CA

Maurizio Scarpa, M.D., Ph.D.
University of Padova, Padova, Italy

Elizabeth Yuko, Ph.D.
Fordham University, Bronx, NY

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

The Conversation

Erika Berg (*host*):
Healthcare access is a global challenge, compounded for rare diseases, in which diagnostic and treatment options may be both geographically and financially out of reach for many patients. Yet, access is attainable. Today we will be exploring strategies to overcoming obstacles to access with our fantastic panel, which includes people with lived experience as well as experts in biomedicine, policy, and bioethics. I would now like to take the opportunity to welcome our panel.

Elizabeth Yuko:
I am a journalist and a bioethicist.

Jeromie Ballreich:
I am an associate research professor at the Johns Hopkins Bloomberg School of Public Health.

Elizabeth Currid-Halkett:
I am professor of public policy at the University of Southern California. My son Elliot was treated with gene therapy for Duchenne muscular dystrophy about a year ago.

Maurizio Scarpa:
I am a pediatrician and a professor of pediatrics at the University of Padua. I lead a regional coordinating center on rare diseases in Udine University Hospital, in Italy. I am also coordinator of the European Reference Network for Hereditary Metabolic Disorders (MetabERN) here in Europe. Thank you for the invitation.

Erika Berg (*host*):
I am going to put the first question to Elizabeth Yuko. What does it mean to have good access to healthcare?

Elizabeth Yuko:
My wish list? Well, to start with, healthcare that is affordable and that people can pay for and access without going into debt or having to make serious decisions about whether they are going to fulfill other basic needs. It should be geographically close and accessible. Also, if you have a condition, rare or otherwise, you should be able to get a diagnosis in a reasonable amount of time, and not wait years or even decades to get a diagnosis. Having a treatment available that can ideally be curative, but if not, at least help mitigate the symptoms, is also important. I would also add patient-centered approaches by the healthcare professionals, trauma-informed care, reproductive healthcare, and mental healthcare…I could go on and on, but I will stop there.

Erika Berg (*host*):
Thank you. Now that we know what good healthcare access is, Jeromie, could you please share from your perspective; what the unique issues are that people with rare diseases face when attempting to access healthcare?

"People with rare diseases represent, as the name implies, small populations. In economics, when you have a small population the treatment usually requires a price with a high premium, or a high price point, therefore making it very expensive to get access to the innovative treatments. I would also add that people living with rare diseases face geographic issues, as oftentimes these cutting-edge treatments are only available at select treatment centers. You may have to travel and then that raises issues about socioeconomic disparities."

Jeromie Ballreich:
That is a great question. Outside of the clinical aspect, one of the big areas is affordability. People with rare diseases represent, as the name implies, small populations. In economics, when you have a small population the treatment usually requires a price with a high premium, or a high price point, therefore making it very expensive to get access to the innovative treatments. I would also add that people living with rare diseases face geographic issues, as oftentimes these cutting-edge treatments are only available at select treatment centers. You may have to travel and then that raises issues about socioeconomic disparities. I think the main obstacle or main struggle point has to be affordability.

Erika Berg (*host*):
Maurizio, I know you did a study where you were looking at healthcare access in the rare disease space across the globe. I was wondering if you could share with us, if there are some places around the globe, or even countries or regions that do better with respect to healthcare access and rare disease. If so, what do they do differently and what can we learn from them?

"… there are definitely places where rare diseases are better treated than others. […] What we noted was that the best countries, in terms of access and where the management of patients is actually pursued, are the countries where there is a national plan for rare disorders."

"In the United States, the Orphan Drug Act, signed in 1983, was more or less the Magna Carta for other plans addressing rare diseases. In Europe, since the year 2000, we have had different plans. We had the European Commission plan for rare diseases, which obliged all the member states to draft a plan for rare diseases. Now, since 2017, we have a new initiative, which are the European Reference Networks."

Maurizio Scarpa:
I think that globally, there are definitely places where rare diseases are better treated than others. Last year, as you said, we produced a publication on the global situation of all rare disease patients, with respect to diagnosis, management, access to therapy, and to research. We found great variability, like leopard spots, where here and there, even within the same country, there were different solutions, different burdens, and different ways of approaching the disorders and the difficulties. What we noted was that the best countries, in terms of access and where the management of patients is actually pursued, are the countries where there is a national plan for rare disorders. Where there is a governmental or central guidance for the centers on how to treat patients and on how to have access to therapy. This means that there is awareness about rare diseases and a full collaboration with patient associations and stakeholders in order to attract attention to rare diseases. Although there are 6000 to 7000 rare diseases, they are still forgotten, especially after the Covid-19 pandemic, I have to say. Countries where things were working very well were also those where we could find patient registries, maybe even national registries, in order to have epidemiology and statistics regarding the frequency and incidence or prevalence of rare diseases. This is extremely important because we can then develop natural history studies and we can promote drug development. Of course, we found countries where everything was not available and there are places in the world where there are still black holes regarding rare diseases. The United States and Europe are the two places, together with Australia, where the treatment for rare diseases has a long history.

In the United States, the Orphan Drug Act, signed in 1983, was more or less the Magna Carta for other plans addressing rare diseases. In Europe, since the year 2000, we have had different plans. We had the European Commission plan for rare diseases, which obliged all the member states to draft a plan for rare diseases. Now, since 2017, we have a new initiative, which are the European Reference Networks. This is a strategy that I think is extremely successful. I am leading one of them for metabolic disorders, and we are gathering all the centers of excellence from the various member states together to work towards improving patient care, while keeping the patients at the center of everything we do. For example, the metabolic ERN, which I coordinate, is comprised of 100 centers of excellence, which are recognized by the local ministries of health and went through a very complicated procedure of quality assurance and standard assessment. They are working together in all of the 27 member states, as well as the UK, because we did not exclude the UK even after Brexit. I think that the awareness, the national plans, and the registries,

are the key points to work on. We need to help places like Africa, China and India, which are growing very well in terms of rare disease initiatives, so that they align with the other countries and continents in order to have a global homogeneity when it comes to diagnosing and treating patients.

Erika Berg (*host*):

Great, thank you. Elizabeth, can you share your story about how you gained access to this gene therapy for your child and tell us your personal story on that?

Elizabeth Currid-Halkett:

My son Elliot was diagnosed with Duchenne muscular dystrophy in January 2020. He was, I think, seven months old and it was a month before the pandemic. It was a very dark time. I am a professor by trade, so the first thing I did when I got this diagnosis was I just started doing lots and lots of research. Research finds the answer. Everyone I talked to talked about this doctor at Nationwide Children's Hospital, saying, "Have you heard of Jerry Mendell? He is a neurologist and he is working on gene therapy". I did not know what gene therapy was. This is all science fiction to me. My story starts with doctors who engage despite how prestigious they are or how busy they are. When I emailed Doctor Mendell, I did not expect a response, but I got one 4 hours later. Then he got on the phone with me and he said, "I have these trials running with these young boys, and we are doing well. These trials are looking really good." Even in the early days of grieving this diagnosis, I had this hope. I am an inveterate believer in science. Hearing this, I thought, "Okay", and I just started following these trials.

> ***"I knew there were three roadblocks. The first was the FDA approval, and they gave a very limited approval initially, and then a broad approval in June […] the next one would be, as is the case with all gene therapies, making sure you do not have antibodies to the virus they use to deliver the treatment. […] that was hurdle number two. Hurdle number three was insurance. I knew this was not going to be cheap, and indeed, I was not wrong. It is a $3.2 million gene therapy. It is the second or third most expensive drug in the world. At the time, it was the second most expensive, and I had no idea how we were going to do this."***

The reason I bring this up as a start of my story is that when the FDA did give accelerated approval for Elevidys, which is the gene therapy my son got for Duchenne muscular dystrophy, I was ready to go. I had been following the trials. I had been looking at the numbers. I had seen their ups and downs, but I was ready. I knew there were three roadblocks. The first was the FDA approval, and they gave a very limited approval initially, and then a broad approval in June. Then I knew the next one would be, as is the case with all gene therapies, making sure you do not have antibodies to the virus they use to deliver the treatment. We actually kept my son out of preschool because I wanted no possibility of him getting these antibodies, and he did not have them. That was hurdle number two. Hurdle number three was insurance. I knew this was not going to be cheap, and indeed, I was not wrong. It is a $3.2 million gene therapy. It is the second or third most expensive drug in the world. At the time, it was the second most expensive, and I had no idea how we were going to do this. I worked with my insurance and my son's local doctor, Dr. Ramos Platt from Children's Hospital Los Angeles, who was like a pit bull in the way that she fought with me. We put together the papers and she spent all her time getting this to happen. Then, when my insurance authorized it, it started to stall. This is where my story deviates from other parents' stories. When my insurance started to stall and my son's doctor called me and said, "I do not know what is going on, but I think it is on the insurance end." What does a normal parent do? They lift their hands up and they say, "I do not know. I guess we are just going to have to wait and hope." However, I am a professor of public policy, and down the hall from me are some of the best health economists in the world. My dean is a health economist who knows insurance inside out. What did I do? I contacted him and I said, "I am having some problems with insurance. I am wondering if you can illuminate." And he did. I work at an incredibly benevolent institution where, when I reached out to anyone I knew who worked in administration and said, "I need help and I do not know what is going on," they were able to help. Elliot did get treated, three weeks later. On the day we had booked an infusion room for him, it was ready to go, and he was treated.

A year later, it is like he is a different child. It is such an extraordinary treatment for my son. He received it so well. However, the feeling that I have afterwards is not just one of immense gratitude and relief but I also have the thought, "What if I did not have those resources at my disposal? What do other parents do?" For me that is the biggest challenge and the one we must solve. It just should not be this hard. It should be a human right to have access to this kind of treatment.

Erika Berg (*host*):

Amazing story, thank you for sharing. If you do not mind me asking, what was the trick with the insurance?

Elizabeth Currid-Halkett:

It got locked up in the management component of the health insurance, where they blocked it and it got unblocked. I do know all the mechanisms that were released to make that happen, but I alerted the people who did know, and that, again, was a really byzantine process. I would not have been able to do it without contacting people who knew how it worked, and I do not think that is straightforward for most parents.

Erika Berg (*host*):

Maurizio, what have you learned as a clinician about getting healthcare access for your patients with rare disease? What is your role as a clinician in that process and what have you observed as far as your patients who are trying to get access to care?

"I think that one of the most fascinating things that a man can do is to give therapy to a sick child. Indeed, whenever I can give even a tentative treatment to a rare disease patient, I am the happiest person. I am the saddest person, when I think about the 95% of other patients who will never receive therapy because we do not have therapy for them. This is the frustration that we are experiencing as clinicians every day, more or less, because for one patient that can have therapy, we have another nine for whom we can only offer a diagnosis and then a follow-up. This is the first thing. The second point is that we really need to give the patient the right to access therapy."

Maurizio Scarpa:
I think that one of the most fascinating things that a man can do is to give therapy to a sick child. Indeed, whenever I can give even a tentative treatment to a rare disease patient, I am the happiest person. I am the saddest person, when I think about the 95% of other patients who will never receive therapy because we do not have therapy for them. This is the frustration that we are experiencing as clinicians every day, more or less, because for one patient that can have therapy, we have another nine for whom we can only offer a diagnosis and then a follow-up. This is the first thing. The second point is that we really need to give the patient the right to access therapy. I am happy that we are living, at least here in Europe, in countries where the access to treatment in most cases is insured. In Italy, by law, we have the right to access any kind of therapy which is available on the market without any selection. I am a little bit frustrated by the fact that there are other countries, even here in Europe, who economically speaking, do not have the possibility of giving therapy to patients, although they would like to. This gives rise to a very big discussion on the inequalities in patient treatment and the fact that depending on where you are born, you can either have access to the therapy or not. This is something that clinicians have to battle with, and it would be extremely important to have an economic solution in order to give the patients therapy. I just came back from an incredible tour in India, where I was lecturing in a lot of hospitals. I was very much frustrated by the fact that in India, they have a fixed amount of money per life that can give access to a therapy for only six months to a year, and then that is it. I think that there is quite a lot of work to do altogether with policymakers, clinicians and patient associations, in order to find a way to provide therapy to all the patients. One major problem is also trying to convince the industries not to have this huge price for therapies, which is a problem that is never discussed enough, because that is also one of the major issues and obstacles for countries wishing to provide the therapy. I think that we should find a way to give the democracy of therapy to our patients and ensure the right of therapy to all patients that need it.

Erika Berg (*host*):
Great, thank you. Elizabeth, these innovative therapies like gene therapy and cell therapy are brimming with promise for people with rare disease, but there are still only a handful of these types of treatments. What is holding back the development of innovative treatments for people with rare disease? Is there enough research and development (R&D) in this space so that we could at least get to the point where there are therapies available?

Elizabeth Yuko:
Money plays a role in that as well because if pharmaceutical companies do not think that they are going to make the money back, and then many times over, there is not much of an incentive for them to put the money into the R&D. Beyond that, with certain rare diseases, like sickle cell disease, for example, you have other systemic issues at play. I think there are roughly 100,000 people in the United States living with sickle cell disease, and the vast majority of them are of African descent, although there are people of other ethnicities who have sickle cell. This is something that Harriet Washington writes about in her book Medical Apartheid: how sickle cell has been classified as a black person's disease for decades or for over 100 years at this point, because the sickle-shaped cells were first identified in 1910. Then in 1949, sickle cell disease was the first disease examined on a molecular level. By all accounts, it should not have taken until the end of 2023 to have these curative treatments approved. So that, unfortunately, is a part of it. Along the same lines, it is probably also underdiagnosed because some members of the medical profession might ignore the pain of Black Americans, for example. Therefore someone who may be living with sickle cell disease may not receive that diagnosis and then may never get that treatment, and they are not getting included in the numbers of people who need that type of treatment. It is a big cycle.

Erika Berg (*host*):
Jeromie, someone mentioned the Orphan Drug Act, and if my memory serves, it is an act to help bridge that divide and help spur research and development for these innovative therapies. I was wondering if you can talk a little bit about policy and how that maybe helps or what else can be done?

"In 1983, Henry Waxman was one of the original sponsors of the Orphan Drug Act. It is really a remarkable piece of legislation. It helps spur development into rare diseases. It provided tax credits for companies to do R&D. It also provided market exclusivity. So when a drug became approved and commercialized, the company could make back their money."

Jeromie Ballreich:
In 1983, Henry Waxman was one of the original sponsors of the Orphan Drug Act. It is really a remarkable piece of legislation. It helps spur development into rare diseases. It provided tax credits for companies to do R&D. It also provided market exclusivity. So when a drug became approved and commercialized, the company could make back their money. In pharmaceuticals, you have a tremendous, high-risk investment upfront, and you only recoup that if a drug gets approved, and getting approval is a dice roll, to say the least. There are a lot of hurdles, from laboratory science to actually getting it working in a human body and being safe and effective. The Orphan Drug Act has been around and had a couple of changes with the President Trump era tax cuts where they reduced the R&D tax credit by a little bit, but market exclusivity is still a major component. Outside of that, there are several other areas of policy. Elizabeth Y. mentioned sickle cell disease. This is an area where President Biden, back in October 2022, tasked the Centers for Medicare and Medicaid Services (CMS), to look at access programs for high-cost drugs. Last year, we had two gene therapies, exa-cel and lovo-cel, approved for sickle cell disease. CMS is now working to develop a policy model called the Cell Gene Therapy Access Model, looking specifically at those two drugs, where they will partner with Medicaid programs using innovative payment. The idea is to improve access, because this is a population, as Elizabeth pointed out, which is disproportionately African American. It is also a population disproportionately covered under Medicaid, which, for the audience who may not know, is a public payer in the United States but it is also one of the more financially constrained payers. There are policies at the federal government level and there are also a number of state initiatives to try to spur research and development in rare diseases. California had a big stem cell initiative. There are also additional policies in terms of ensuring that when a treatment gets to the market, that people have access, and that is not only beneficial to the patients but it is also beneficial to industry because they want to be able to sell the drug and access is how they sell the drug.

Erika Berg (*host*):
Elizabeth C-H, when you first learned about the gene therapy for your child, it was still in clinical trials. I was wondering if you could talk a little bit about how the FDA decision impacted your ability to access that treatment and how that plays out with your insurance coverage.

Elizabeth Currid-Halkett:
The FDA has a mechanism for approving treatments prior to the phase III results coming through, and it is called accelerated approval. If my memory serves me correctly, I think that Elevidys, the gene therapy for Duchenne muscular dystrophy which Elliot received, was the first treatment under accelerated approval. Now, this is an amazing mechanism to get these life-saving treatments to a patient population as soon as humanly possible because, with progressive degenerative diseases like muscular dystrophy, if you get the treatment at four versus five or six, there is a big difference in how you receive it. Even if it is effective across age groups, it is most effective when you get it early. Elliot really benefited from that and my insurance company did actually approve treating him. However, I have heard multiple stories that accelerated approval is also a loophole for insurance companies to say, "This is investigational. It is also really expensive and investigational. So we are going to go ahead and wait until it gets broad approval." That is the problem: it is actually a double-edged sword. On the one hand, it is the way that the FDA approved this accelerated approval, because it allows this treatment to reach patients. However, on the other hand, insurance companies can say no until it is fully approved, and that can take a lot of time. It took about a full year from accelerated approval, when Elliott received it, to broad approval.

Erika Berg (*host*):
With the accelerated approval, did you have any safety concerns, or did you decide to just go for it? I want to talk a little about the safety issues with experimental treatments.

Elizabeth Currid-Halkett:
Elevidys is a very safe treatment. There have been other problems with other trials, for sure. One of the things that was very reassuring about Elevidys was that the only thing I needed to look out for was efficacious treatment, not safety. Safety can be an issue, but I think that is one of the things the FDA is very focused on. I was not super worried about that.

Erika Berg (*host*):
Elizabeth Y., from your bioethics background, what can you tell us about what we should be thinking about when giving access to an experimental treatment?

Elizabeth Yuko:
If there are approved treatments for a rare disease that a patient might not be able to afford, and then they are also given the opportunity to take part in a clinical trial or try an experimental treatment, they are then in the position of having to weigh the potential risks and benefits of this treatment. Safety is certainly one of them, especially in the earlier stages of research when the safety profile is not as well known. A patient and their family may be forced to make the decision of, "Okay, if I cannot afford this drug, should I try this experimental one, which might or might not work. Should I offer myself as a research subject?" Of course, that depends on many different factors, including how advanced someone's condition is. It is this additional level of complication that some people have to face when they are given that option, and they are not always going to work. As Jeromie mentioned before, there are so many experimental treatments that never make it to market and never get approval that we just do not know about. Even though it is not something we hear about on the news a lot, it is happening. Behind those trials are people who have had to make those decisions and have weighed the risks and benefits of each treatment.

Erika Berg (*host*):
I think we have been a little US-centric. Maurizio, I was

wondering if you could talk about how this works in the European model. For innovative therapies, is it the same sort of clinical trials and accelerated approval approach, or do you have your own model?

> ***"As I said, the frustration is actually to see that unfortunately, the clinical trials for rare diseases, in particular, are made up of only a few patients. The selection for a clinical trial is very strict. Most of the time, a lot of patients are excluded from the clinical trial. There is a frustration for the family and for the patients when they are not included."***

Maurizio Scarpa:
I think that the model is more or less the same with different timings and with different approaches regarding some local regulations. The clinical trial per se is a very standardized procedure. Regarding safety, as clinicians we cannot try any substance without a proper project or experiment being run first both pre-clinically and then in the clinics. Then there are all the procedures of phase I, phase II, phase III, and then phase IV, after marketing authorization. Even during the post-marketing phase, there is the need to follow the safety and efficacy of the therapy with patients. As a clinician, I feel very confident that when there is a new drug to be tested, that all the toxicology data and all the safety data, at least at the clinical level, have been collected. There is a very rich documentation about that. There are a lot of publications before starting a clinical trial, even for off-label or repurposed drugs. There is now a lot of drug repurposing because we have so many millions of drugs that were not successful for the original disease, and can now be shifted to treat another disorder. In my opinion, even that is safe because all the toxicology and safety data have been collected, including data from human trials for the diseases for which the therapy was originally studied. As physicians, we are really devoted to the safety of patients. We will never harm a patient. We will never do anything that could worsen the patient's condition. As I said, the frustration is actually to see that unfortunately, the clinical trials for rare diseases, in particular, are made up of only a few patients. The selection for a clinical trial is very strict. Most of the time, a lot of patients are excluded from the clinical trial. There is a frustration for the family and for the patients when they are not included. When the clinical trial is finished and there is an idea that it is working, sometimes we do not have the time before approval to give the drug in a compassionate way. So the patient has to wait until the drug is on the market. The period between the publication of the clinical trial results and the approval of the drug can vary significantly, depending on the country. The patient might want to receive the drug, but they cannot because there is not a compassionate use program available. Then whenever there is approval, there are accessibility issues related to the member states or to the state economy. As you see, there are a lot of obstacles that are actually preventing the patient from having the opportunity to receive the therapy. I think that globally speaking we should really find a way to have connections between the different agencies and researchers, and the possibility of whenever the drug has been found to be safe, and eventually efficacious, to find a way to allow the patients to enter in a compassionate use program up until when the drug is on the market. We desperately need therapy for these patients and we must try to shorten, as much as possible, the time needed for patients to access therapy.

Erika Berg (*host*):
I am curious, for clinical trials for rare disease treatments, are there typically geographic limitations on who can be included in those trials or are they typically open to anyone with that disease, or does it vary?

Maurizio Scarpa:
Unfortunately, I have to answer yes, there are. First of all, whenever you start a trial from scratch, you need a phase I center. A phase I center is a center in which you can really test a previously untested drug on a patient. All of the preclinical testing has been done, but you always have a doubt that something can go wrong. You need specific equipment and you need a specific clinical trial team that is prepared for any kind of serious adverse event that could occur in a patient. We need phase I trial centers. Phase I trial centers are not distributed worldwide in a very homogeneous way. Even in Europe, we have quite a lot of phase 1 trial centers. However, what is usually directing the access is actually the decision of the sponsor or the company. If it is a drug from a sponsor or a company, they usually prefer to have the clinical phase 1 trial center in the United States before Europe. For example, there are a lot of drugs that start in the United States and then we have them in Europe and then they reach the other side of the world.

Of course, it is not only dependent on the availability of a phase I trial center but also the availability of patients. As I said, the number of patients for clinical trials in rare diseases is minimal. You can even have a trial with four, five, or 10 patients as a whole. So you need to also find where the patients live and figure out how they can access the hospital. Then, of course, there is the expertise of the different centers participating in the clinical trial. Many factors influence the decision to either start a completely new drug trial or to expand the number of patients tested globally. Usually the centers that are selected are the centers with major expertise. In Europe, we are part of that, and in our network we have all of the centers needed for this and we indeed have the possibility of treating patients.

Erika Berg (*host*):
I want to stick to the geography issue a little, because I think it is one of the major obstacles to healthcare access. We talked about this before, but in May of this year at Children's National here in Washington, DC, the first patient began sickle cell gene therapy after it was approved by the FDA. Many people had received the drug in clinical trials, but this was the first person to get it after they were approved here in DC. It is a therapy that costs millions of dollars, similar to the drug that Elizabeth's child received. Millions of people have sickle cell disease across the world, so it could cure millions of

people, but will it? What are the financial and geographic issues to consider? Now that the FDA approved this drug, do people have to come over here if they wish to receive it or if they can afford it? What are the issues at play?

"If we are developing these treatments that are costing millions of dollars, we are essentially leaving out the rest of the world that cannot afford them, and even many people in the United States who cannot afford them, and saying that certain groups are more deserving of treatment than others. And that is certainly not the case. One of the main principles of bioethics is justice: that the benefits and burdens of research are shared. That is not happening if people are unable to benefit from emerging treatments."

Elizabeth Yuko:
Not to keep going back to affordability, but a treatment can only be as effective as it is accessible. There are millions of people living with sickle cell disease. The highest percentage of people living with sickle cell disease is in the African continent. There are also large populations in the Middle East and Southeast Asia and in lower and middle-income countries. They might not have the medical infrastructure to be able to treat patients with these innovative gene therapies, for example. So, cost aside, that is one issue, but you cannot ignore that. If we are developing these treatments that are costing millions of dollars, we are essentially leaving out the rest of the world that cannot afford them, and even many people in the United States who cannot afford them, and saying that certain groups are more deserving of treatment than others. And that is certainly not the case. One of the main principles of bioethics is justice: that the benefits and burdens of research are shared. That is not happening if people are unable to benefit from emerging treatments.

Erika Berg (*host*):
Jeromie, you mentioned this briefly, but I was wondering if you could talk more about the Cell and Gene Therapy Access Program. What is it, who might benefit from it and how can people learn more about it?

Jeromie Ballreich:
Absolutely. For what we call payers, this is Medicare, Medicaid, health insurers or, if you are in Europe, some of the governments where they are the major payer for your healthcare, what they are looking at are unique payment models. Not just simply pay per pill, but thinking about models where they make agreements with the drug company that if the drug delivers what it was shown to do in a clinical trial, they will pay. However, if it does not deliver quite exactly as expected, they will pay a little bit less or impose a penalty. This is important in rare diseases, because when it comes to clinical trials, one, they are really small, and two, they are also fairly restrictive in terms of which patients can access them. For the sickle cell disease trials, if you had any number of comorbidities you were excluded from being eligible for the trial. So the drug is approved in this more ideal patient population and then sold or marketed to a larger population. When the payers are looking at one million or two million dollar price tags, they want to make sure they are getting their value, and this is where unique payment models can take place.

The Cell and Gene Therapy Access Model is a unique payment model, technically called the outcomes-based agreement model, where Medicaid is working with the manufacturers of exa-cel and lovo-cel, the two gene therapies for sickle cell disease, to ensure that Medicaid patients can get access to these drugs but at the same time show that these drugs do what they should do or what they demonstrated to do in the clinical trials. It really ensures that the healthcare system is getting the value that is expected when you pay a couple million dollars for the treatment.

Erika Berg (*host*):
Is this in effect now?

Jeromie Ballreich:
It is not in effect yet. Well, the access program is in effect, but they are still going through the process. Patients are not getting access to this drug yet through the access program. I believe CMS is expected to have patients getting access to this drug next year under this program. I personally think it is a very aggressive timetable, but we will see.

Erika Berg (*host*):
So under that, Medicaid recipients could have access to sickle cell gene therapy?

Jeromie Ballreich:
If their state opts to agree with this. We talk about geographic issues, and this is a situation where your zip code and your state can determine what drugs you have access to, unfortunately.

Erika Berg (*host*):
Is there anything similar happening in Europe in terms of programs that are helping people to gain access to cell and gene therapies, Maurizio? Or is it also a very local decision?

Maurizio Scarpa:
It is a local decision. We are working at the European level. There is a big discussion on cell and gene therapy access. Of course, the cost of this therapy is really something we need to discuss. There are quite a lot of discussions inside the European Commission and the European Union with stakeholders in order to find regulations and recommendations at the central level for all the member states. However, the single member states have the authority to decide for their country. This is where the trouble comes because, of course, as it depends on the economy, the number of patients, the activity of the patient associations, and

the expertise of the different centers. When you are speaking about gene therapy, we are ready to have patients travel cross-border, because, you cannot administer a gene therapy drug or treatment in any kind of hospital, or a very peripheral hospital. You need to have an expert center. What we are thinking about is to elect some centers per country who will administer this therapy, and ideally numerous centers in order to decrease as much as possible the burden of travel for the patients. There are quite a lot of discussions on this topic.

Erika Berg (*host*):

With all these therapies that are emerging, there are going to be more and more of these very expensive but amazing treatments available and I am sure people with rare diseases would love to have access to these life saving therapies wherever they are. Elizabeth C-H, I was wondering if you could share your thoughts on how people and caregivers in rare disease can advocate for healthcare access?

"When Elliot was treated, I moved from feeling like the most unlucky person in the world to the luckiest person in the world, and I felt a tremendous duty to give back. I wrote this essay for The New York Times about my experience. It got a lot of attention and, in fact, some of my colleagues had not even known what our family was going through until they read that essay."

Elizabeth Currid-Halkett:

I was really moved by some of the comments made by Jeromie and Maurizio, because there is this other layer of geography and disparity that is at play, which is cultural and social capital (this is my area of research when I am not advocating for my son). Even to get access to a trial, you have to be affiliated with a major research center, or have a doctor who is really in the know of where these trials are going. You also have to have a job that is somewhat flexible. With Elliot, he got the treatment under approval, he was treated and he has follow-ups. It is very different when you are in a trial where you have to be evaluated every few weeks, or every month, and you have to travel. That is not only a financial burden, but it is also dependent on the network in which you have healthcare, the doctors you work with, and the time you have on your hands. I wanted to add that to the conversation as it is also complicated in ways that are somewhat nebulous and very hard to track.

"If you have been so lucky to be blessed by science and to have had a good experience you should try to help others have that experience too, using whatever platforms or avenues that are available to you."

When it comes to getting access, this issue is not just limited to Duchenne muscular dystrophy and Elyvitus. When Elliot was treated, I moved from feeling like the most unlucky person in the world to the luckiest person in the world, and I felt a tremendous duty to give back. I wrote this essay for *The New York Times* about my experience. It got a lot of attention and, in fact, some of my colleagues had not even known what our family was going through until they read that essay. For me, I thought, "The system, the treatment and science worked for you. This is your time to give back." What I say is, "You have a voice and can use it. You also can help other patients and parents". One thing I have been very clear with, particularly with my son's neurologists at Children's Hospital, is that if there are parents navigating insurance and they need help, to give them my phone number, because I am happy to give any time that they need to help them write their letters or go through things. You have got to give back in that way. The other thing is that these agencies, like the FDA, they want to hear from you. I have e-mailed Peter Marks, who is the head of the center that approves gene therapy in the United States, in the FDA, and I have e-mailed him multiple times. I do not believe that my voice is disproportionately influential in any way, but I think every bit counts. When Elliot was treated, I was able to say, "Hey, Doctor Marks, my son is doing really well. I know you are considering this treatment. If you need any more information or evidence of how this is effective for many boys, here is another video of my son running and jumping." I think that is what you can do to help others. If you have been so lucky to be blessed by science and to have had a good experience you should try to help others have that experience too, using whatever platforms or avenues that are available to you.

"We need years to study the patients and so we also need the companies to embark in long-term studies for the drugs and not finish when the drug is on the market because that is the moment where the drug is showing whether it works or not, when it is used by the largest number of patients possible."

Maurizio Scarpa:

I appreciate very much what Elizabeth C-H is saying and it is extremely important to collect all the patient-related outcome measures that can really demonstrate the efficacy of the therapy. This is something that is stimulating a very big discussion in Europe and worldwide regarding the patient-reported outcomes measures (PROMs) and patient-reported experience measures (PREMs). I think that it is not only a number or a biochemical measure that determines whether the therapy is indeed working or not, but rather the experience and the quality of life (and the changes of the quality of life) that are extremely important for the patients. Nevertheless, I think that we need to have more science in the clinical trials. We need to start working extremely hard to search for biomarkers, because while it is true that the therapy can change the quality of life without showing significant biochemical effects, it is also true that some biochemical effect might occur before clinical improvement is observed. This is why

we really need to conduct a lot of scientific research, including basic studies, in order to better understand the pathophysiology of the disorder. We want to understand what the best biomarker is for use before the treatment, during the treatment, and during the follow-up period. Then we can really have a full understanding of the safety and efficacy of the drugs. We have to remember that, unfortunately for us, the drugs are not only few but they are also very new. I do not think that all the efficacy of the drugs have been studied yet. We need years to study the patients and so we also need the companies to embark in long-term studies for the drugs and not finish when the drug is on the market because that is the moment where the drug is showing whether it works or not, when it is used by the largest number of patients possible.

"Sharing information, whether you are doing so as a caregiver or as a patient, with other people who are going through something similar, is hugely valuable for other people. It is such a great way of using what you have learned to help other people."

Elizabeth Yuko:
To jump off of what Elizabeth C-H was saying, living with a rare condition can be a very lonely existence. Sharing information, whether you are doing so as a caregiver or as a patient, with other people who are going through something similar, is hugely valuable for other people. It is such a great way of using what you have learned to help other people. I think that it is so great that Elizabeth is doing that for other parents. I was involved in the caregiving of someone with a rare disease who is no longer here, but that was one thing that she loved to do. Any opportunity to help anybody else going through something similar was beneficial for her mental health as well.

Erika Berg (*host*):
We have talked about reaching out to the FDA or working with other families, and we have talked about the Cell and Gene Therapy Access Program that is still in its early stages. Are there other programs and are there ways for advocates to reach out to government and members of Congress who are involved in these sorts of decisions? What should they be focusing on and what policies should we be spending our time advocating for?

"I have seen projections where there are going to be between 20 to 30 gene therapies approved every year going forward. We are going to start seeing a lot of new drugs for a lot of rare diseases. I think it is a situation where patients, caregivers, and parents, you want to be informed about what is out there and you want to advocate, to make sure that once a drug gets out there, it is affordable."

Jeromie Ballreich:
That is a really great question. I testified earlier this year in front of Congress on policies for rare disease, and I believe there were around 23 different legislative proposals that touch upon rare diseases. Some of them were just obvious. For example, one of the big issues is if you had Medicaid and you lived in Ohio, but the only hospital that offered a certain unique therapy was in Maryland and Ohio Medicaid said, "Sure, we will pay for it," they needed to make sure the Maryland doctor and the provider would be enrolled in Ohio Medicaid provider networks, which can take time. For parents and for patients, time is incredibly valuable. There was a legislative proposal to streamline that. There are some obvious policies out there to improve things. Once it is bipartisan, it is just a matter of actually getting the policy approved and signed into law and these little things can help improve access. I think also in general, when we think about access to rare disease, we are really just now beginning to benefit from the tremendous investment, of $5 billion to $10 billion, that was done at the Human Genome project back in the 1990s. We are now beginning to reap those benefits. I have seen projections where there are going to be between 20 to 30 gene therapies approved every year going forward. We are going to start seeing a lot of new drugs for a lot of rare diseases. I think it is a situation where patients, caregivers, and parents, you want to be informed about what is out there and you want to advocate, to make sure that once a drug gets out there, it is affordable. ■

Workplace wins: Finding a fulfilling career and overcoming stigma in rare disease

For many, a career can contribute significantly to a sense of self and purpose. People with rare diseases are no different, yet ignorance, stigma, and accessibility issues can present obstacles to a fulfilling work life. In this discussion, we'll hear from people who have successfully navigated workplace complexities to establish fulfilling careers while living with a rare disease. There are laws in place to protect people with disabilities in the workplace, and we'll delve into what those laws say and how to exercise your rights. We'll also discuss ableism and disability technology.

In this webinar, participants will:

- Hear from those who have successfully navigated careers in the context of rare disease
- Learn about laws that protect people with disabilities in the workplace
- Explore the concept of ableism and disability technology in society.

Panelists

Elizabeth Caldwell, B.S.
Clemson University, Clemson, SC

Dan Jacobs
American Chef, Entrepreneur, and Advocate, Milwaukee, WI

Ashley Shew, Ph.D.
Virginia Tech, Blacksburg, VA

Bonnielin Swenor, Ph.D., M.P.H.
Johns Hopkins, Baltimore, MD

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

The Conversation

Erika Berg (*host*):
For many, a career can contribute significantly to a sense of self and purpose. People with rare diseases are no different, yet ignorance, stigma, and accessibility issues can present obstacles to a fulfilling work life. Today we are talking to some amazing people who have successfully navigated the complexities of working in a lab, a university, and even a reality cooking competition, all while living with a rare disease. I would now like to take the opportunity to welcome our panel today.

Elizabeth Caldwell:
My name is Elizabeth Caldwell and I am currently a senior genetics major at Clemson University. My story with rare disease and disability started seven years ago, when I was diagnosed with a disability. At the time, it was considered a rare disease and it really impacted the way that I viewed research and the world in general. I later learned that it is more prevalent than originally believed and it is actually just severely underdiagnosed and understudied. This experience has significantly shaped the way that I view the world and has also influenced my passions and interests.

Bonnielin Swenor:
I am the founder and director of the Johns Hopkins Disability Health Research Center and the endowed professor of disability health and justice at Johns Hopkins. My relationship with rare disease is that I have a rare retinal condition which started when I was 25 years old, as I was applying to graduate school. That experience shaped my research career and really informs the work that I do as a researcher and that my center does. The work we do involves using data to advance equity for people with all types of disabilities, including people with rare diseases. It really focuses on making workplaces, including science and research workplaces, more inclusive for people with disabilities.

Ashley Shew:
I am an associate professor at Virginia Tech and I do humanities-based research on science and technology. History and philosophy of technology are my research areas, and their interface with biotech, in particular. I am multiply disabled from what is considered a rare cancer, but once you have a cancer, you meet a lot of people with that type of cancer through social media and other sources. So I do not think of it as particularly rare anymore but I have the long-term effects and I have had two recurrences of that cancer. So navigating many of the workplace issues faced by people with rare diseases is something I have found myself thinking about, perhaps along with them, more than I expected to at the outset of my career.

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"I think the main reason why I went on Top Chef was to inspire people with disabilities to do things that they think is out of their comfort zone."

Dan Jacobs:
My name is Daniel Jacobs. I am the chef-owner of DanDan and EsterEv Restaurants in Milwaukee, Wisconsin. I am a James Beard finalist for Best Chef Midwest. I was also the runner-up on the most recent season (Season 21) of Top Chef. I was diagnosed in 2016 with a rare neuromuscular disease called Kennedy's disease. Kennedy's disease is very similar to amyotrophic lateral sclerosis (ALS) and is a degenerative disease. While working in the restaurants, I have noticed, in the last five or six years, how my body has changed and how I need to adapt. I think the main reason why I went on Top Chef was to inspire people with disabilities to do things that they think is out of their comfort zone. Also, to help them realize that just because someone tells you no, it does not mean you have to take no for an answer.

Erika Berg (*host*):
I am going to put the first question to Elizabeth, but I am hoping we can go around and get each one of you to weigh in, as each of you has a pretty great job from what I am hearing. Elizabeth, can you tell us about how you ended up in your current role?

Elizabeth Caldwell:
I guess my main role right now would be a student at my university. In that role specifically, I am most involved with the undergraduate research component at Clemson. I am very thankful that I have had the opportunity while at Clemson to partake in multiple different research opportunities, all of which have actually included rare disease because I have pursued those, both at Clemson and also at St. Jude Children's Research Hospital. I have been able to really enter the lab and see science through the lens of having a disability while also serving a community that I personally relate to.

Bonnielin Swenor:
I got into this job really because of my lived experience. My journey with disability began right as I was applying to graduate school, and that changed the direction of my research. Going through graduate training and public health, while entering into this community of people with disabilities and rare diseases and learning about it in a very different way, was very informative and pivotal. It made me realize that we need to change the narrative of how we are training, researching, and including (or not including) people with these lived experiences as experts, and make research careers more inclusive. That really shaped the work that I am doing.

"I think people in the rare disease community, in particular, do not know what is out there and do not necessarily think of themselves as disabled from the outset."

Ashley Shew:
I do feel like some of us who are in some of these careers, considering the academic job market, get here by luck somehow. It is not that we are not also talented, but talent is not always enough in a lot of circumstances and is not even what is looked for in others. So I am very lucky to be where I am and I get to work with so many graduate students and undergraduate students at Virginia Tech through our disability alliance and caucus. I became disabled after receiving my cancer diagnosis when I was 30, so I was already in a particular career path. I knew that I needed to find other disabled people. I think people in the rare disease community, in particular, do not know what is out there and do not necessarily think of themselves as disabled from the outset. We ended up forming this disability alliance and caucus. There was interest from some staff members and a number of undergraduate students to organize these things. It has shifted a lot of the ways in which I pursue my own research and how I think about my own classes, in terms of universal design for learning and how to accommodate really unusual situations. It has made me a more creative and better teacher. Regarding the topics I research, I do not think that every disabled person has to research disability, but there is the sense in which the research questions I am really interested in have shifted to more disability-oriented topics, in concert with larger questions about human existence and technology.

Erika Berg (*host*):
Dan, maybe you can tell us about how you entered the kitchen, and then what brought you to your restaurants and then Top Chef.

"I realized that I needed to do more than just cooking. I am not a researcher, and I do not pretend to be, but what I can do is raise money for researchers."

Dan Jacobs:
I think it is a very long road that actually brought me to working in kitchens. At a very young age, I found that I really loved cooking and I could make a career out of it and I think that is a truly special thing. I think people spend their whole lives looking for something like that. I figured it out when I was about 19 years old, so I have been cooking for 27 years professionally. I worked for over 15 years in Chicago, and then my wife Kate and I moved to Milwaukee about 13 years ago. We opened up DanDan eight years ago in July and EsterEv shortly thereafter in November. In the same year that we opened DanDan, I was diagnosed with

Kennedy's disease. I think when you have a rare disease and there is no cure or no magic bullet, you kind of have this moment of denial. I remember the first time my doctor at the University of Chicago told me what I was diagnosed with, I did not really think much of it. The second time I went there, I just assumed that I was going to get a pill that would make everything fine. When you come to that realization that this is not the case, it changes things. I realized that I needed to do more than just cooking. I am not a researcher, and I do not pretend to be, but what I can do is raise money for researchers. So that was where the next path led me. Over the last six years, we have raised over $100,000 for Kennedy's disease research through the Kennedy's Disease Association (KDA) which has been very fulfilling. Also, as you move along, you shift into different roles. I always say that if I am cooking on the line, something has gone horribly wrong. We have really failed at our jobs. I think I have definitely transitioned into more of a mentorship role and R&D position in the restaurants. I have also been able to work in advocacy at our state, local and federal levels, working with groups like the Independent Restaurants Association, No Kid hungry, and World Central Kitchen, just to name some of the big ones. But it has been a long and strange road. Top Chef was something that I had always wanted to do and had thought that I would be really good at. Turns out I was! It was incredibly challenging, but also incredibly rewarding. I am just lucky enough to still be able to do all the things I do.

Erika Berg (*host*):

Ashley, what challenges have you faced in achieving your career goals and how have you navigated those hurdles?

> ***"Luckily, as I work for a university that is a state university, I have pretty good insurance compared to many. I think that is where a lot of people with rare diseases and disabilities really struggle. Remaining constantly employed, when your body is inconstant, is really a challenge."***

Ashley Shew:

I think about what it means to get treatment and deal with fatigue. It is the ho-hum boring things that have impacted my career in significant ways, such as being out on medical leave, getting treatment, facing uncertainty, the scan schedules and having to cope with a lot of unknowns. When people ask, "What is your five year plan for your career?" I think, "I am trying not to die." It is not that exciting. I am going to do a lot of things, but it is also my experiences that have made me like my work. I think my work is fun and good. I enjoy the collaborations that I have going on, but being so sick and having navigated some weird career related things has also helped me prioritize other areas of my life.

Luckily, as I work for a university that is a state university, I have pretty good insurance compared to many. I think that is where a lot of people with rare diseases and disabilities really struggle. Remaining constantly employed, when your body is inconstant, is really a challenge. And I have been insulated in many ways because of the career that I have chosen. I also know of people who choose to work for large state universities in different staff roles because the insurance is better than what they might get at smaller institutions or a private college atmosphere. There are some strategic decisions that I hate that we must make about healthcare. However, those are decisions that people with rare diseases have to consider carefully, especially because a treatment can involve many unknowns. It is often unclear how it will go or how it will affect you, which makes having something more dependable, in terms of work, all the more important. I hate that that is often a choice we have to make. In terms of my own career goals I have been very lucky for the insulation that has allowed me to continue to exist in a job as I continue to exist as a human being.

> ***"I think part of it was just getting over that hurdle of asking for help, which can be a big mental block for people with disabilities."***

Dan Jacobs:

I feel like because of my role as a chef-owner, I am a bit insulated as well. I am lucky enough to have these great teams that are willing to pick up where I cannot. I think that is a beautiful thing about the environment that we have been able to create at the restaurant. It is a very team oriented environment. But it is tough. What I do is extremely physical and I deal with fatigue. I deal with the inability to carry things up and down stairs. I think part of it was just getting over that hurdle of asking for help, which can be a big mental block for people with disabilities. Sometimes you want to do everything and prove that you can do everything, but not at the risk of injuring yourself or those around you. Sometimes you just have to ask for the help. I think we have been really lucky in that way, by having great people around us to lean on.

Bonnielin Swenor:

I would say that I have certainly chosen a path to do work in making STEM, science and research more inclusive for people with disabilities, but in many ways I had to, in order to have a job that I wanted. I think that even now, for people with rare diseases or disabilities, we often have to take that on ourselves. And that is on top of everything else we do. I sometimes think, "What could I do with my research if I just did my research?" But that is just not possible because there are so many aspects, from the environment, to the tools we use, to the stigma, to the bias, that if I did not push back against those things, I would have been pushed out a long time ago. So that work is constant.

Elizabeth Caldwell:

Continuing on Bonnie's point, one thing that I always emphasize to people is that my job is being a student. I am aspiring to a career in medicine and policy. I am a friend, a daughter, and all of those roles. But no matter what, I have to be an advocate. That is a role that, unfortunately, almost everyone with a disability has to take on, whether they want to or not. I think it should take a smaller village to help uplift everyone because our community is dealing with health challenges as well as trying to maintain these other roles. That means we are less physically capable than some

people to advocate for ourselves, but we have to. I think that, as a society, we need to realize that we should uplift those voices, to help remove some of that burden because at some point, we need to be able to fill our other roles in order to feel the most amount of satisfaction. I love being an advocate, but it is because I choose to be an advocate. Some people do not want that life, but they are forced into it. So I think that is something that a lot of people need to keep in mind when it comes to people with disabilities having careers: we have to advocate for ourselves, but having someone step in as an advocate could be very meaningful.

Erika Berg (*host*):

Let us now talk about stigma. Elizabeth, can you talk about a time when you have experienced stigma and how you dealt with that?

> ***"People have now made assumptions that I am not capable of doing certain things or that I am not able to succeed because of my disability. People are able to make those snap judgments before they have even met me."***

Elizabeth Caldwell:

It pretty much started the day that I was diagnosed, I think. It started when I came to school with this large diagnosis of a disability, at the end of middle school. I went to a small kindergarten through grade 12 school, so most of my grade had known me since I was six years old, and I said to them, "I have a disability and it explains what I have been going through." It was almost as if that could not be true. The replies were, "You are so young. We know you. You are so normal. You are active. You are able to play sports. How could you possibly be disabled?" I think that there is so much stigma around the typical vision of a disability, but equally stigma around moving away from that original typical image. I have received a lot of pushback about the validity of my disability and my diagnosis, as I do not look the part.

Now, since coming to college, my disability has progressed and I have started to use a cane full-time, which has shown people that I do need help and accommodations, and that has been helpful. However, the stigma has now shifted. People have now made assumptions that I am not capable of doing certain things or that I am not able to succeed because of my disability. People are able to make those snap judgments before they have even met me. I always like to say that people see my cane before they see me, and I think that is a big thing that we need to change. If we could just stop assuming things about people, whether it is about disabilities or any other identity, we could really open the door to better conversations that could truly improve the lives of people with disabilities.

Dan Jacobs:

I really feel the same way because my disability does not outwardly show, as I hide my braces. I wear baggy pants so that my braces fit underneath them because I do not want to have that discussion. I do not want to have to constantly be informing people. I do have a disabled sticker on my truck, and I will park in a disabled spot. A couple of times now I have had people questioning me as to whether or not I am actually disabled. I should not have to have that discussion. I should not have to explain myself to anybody. I also use a cane and when people do not see me using a cane, they assume that I am fine. In reality, it is just that I am having a good day as opposed to a day where I actually need to use my cane. I agree with everything everyone is saying here. It is tough and I wish it were simpler.

> ***"It is about how people react when they have knowledge about your condition, or when they see you acting in ways they do not expect."***

Ashley Shew:

I feel like there is an extra labor in managing all the perceptions of people around you that does not really get unpacked, whether you have an apparent or non-apparent disability. It is about how people react when they have knowledge about your condition, or when they see you acting in ways they do not expect. I do not know that this is necessarily stigma, but it is about dealing with certain perceptions of who you are, where you belong, or what things you are "allowed" to use or not. The way resources for disabled people are policed by non-disabled people, who think they are heroes (but are not), is really ridiculous. I think the Americans with Disabilities Act (ADA) "swagger tags" in your car are an example of that. I have friends who are afraid to use their disability placards because they do not want be assaulted in a parking lot for not looking disabled enough, even though they are in chronic pain or have breathing conditions that make it very difficult to walk long distances. I get a little bit less of that. They eye me weirdly. When I get out of my car and they see that I am an amputee, they leave me alone, which is a delight. I guess it is because I have a heavy object attached to me that I can detach and throw. So I am somewhat more of a threat, and I appreciate that aspect of my life. This managing of other people's perceptions and expectations, whether you are camouflaging in a particular way or not disclosing because you do not want to enter into a conversation, which is none of their business anyway, is tiring. I wish people would let others be, even if they are doing strange things. People know themselves and their bodies better than strangers in a parking lot.

Erika Berg (*host*):

Is there an official name for this type of bias?

Ashley Shew:

It is ableist expectations or ableism.

> ***"When there are barriers that are not being addressed for people with disabilities, the assumption is that it is of course your disability that is holding you back, not the environment and the structures that have kept you out."***

Bonnielin Swenor:
I think in careers, this bias really holds people back. In many jobs, your ability to move forward in your career depends on how others perceive your ability and competence, or on subjective assessments of your success and potential. Academia is a prime example of that and I am a prime example of that. How many talks have you given? How many papers have you published? How many grants have you received? When there are barriers that are not being addressed for people with disabilities, the assumption is that it is of course your disability that is holding you back, not the environment and the structures that have kept you out.

Early in my career, I was kicked off a project because of my disability, as there was concern that I could not see the data. The leader of the project could not understand how I could contribute and thought that I would make too many mistakes. That was a difficult time for me. I was a junior and I was afraid to push back. I knew very well that even if I did push back, it was not and still is not the kind of discrimination that is well understood or accepted by people in power as being real. There are a lot of questions asked and I knew it would just kill my career. So I did not do anything about it and it absolutely impacted my career. It was on a project that was really central to the work I was doing. So, as a result, I shifted gears and started studying something else entirely, because it had major manifestations on what I could and could not do as a researcher, in terms of the grants I could or could not receive. That is actually more common than I think people realize.

Erika Berg (*host*):
Is there a way to respond when you are being clearly pushed aside because of your disability? What should someone do in that situation?

Bonnielin Swenor:
I think now is the moment where this all needs to change. The individual in question was a very successful, very senior, and very influential researcher. As a "nobody", I did not stand a chance to fight that battle. I do not think that has changed much. To be honest, in many institutions and many workplace settings, if someone is bringing in a lot of money or is successful or high profile, it is incredibly hard to fight that and still come out on the other side with opportunities for a career. We need to think carefully, across all career spaces, about what to do when this happens, how to prevent it from happening and how to create opportunities or structures to take the pressure off and offer support. There was no place for me to go to report this, quite honestly. At the time, that would have made sense **and could** have led to meaningful change. Again, I think this is a type of bias and discrimination that is still not being discussed or thought about as real or as happening in our workplaces, and I think that needs to change.

Erika Berg (*host*):
Dan, as you were saying earlier, you have some physical limitations that might interfere with kitchen work, but I am wondering, has stigma entered into your experience in the kitchen or on a cooking reality show? Are there assumptions made about what you can and cannot do that have impacted your work?

"I was lucky enough to be able to make my own path at the restaurant and implement things that would help me as the chef. What I have learned from this experience is to never discount anybody on our team and uplift the people around us. Regardless of where they come from or if they have a disability, we are trying to make our restaurants a better place for people."

Dan Jacobs:
I was lucky enough to be diagnosed with something when I was already the chef and owner of a restaurant. I think if I had been diagnosed and had started to feel the effects of Kennedy's disease when I was in my twenties then things would have been different. I think I would have had a very similar experience and it would have been very difficult. I do not think people would have understood. The physical limitations would have eventually pushed me into different roles or out of the kitchen, as it is an incredibly physical job. We are talking about being on your feet 12 to 14 hours a day. You are moving a lot and lifting a lot, and on top of that you are adding heat and fire to it all. It is an incredibly physically demanding job and I think it would have been very difficult for me. I was lucky enough to be able to make my own path at the restaurant and implement things that would help me as the chef. What I have learned from this experience is to never discount anybody on our team and uplift the people around us. Regardless of where they come from or if they have a disability, we are trying to make our restaurants a better place for people. Whether it is offering employees health insurance, paid time off, or family leave, we provide it even though we do not get reimbursed for it. I think it is our responsibility to make our restaurant a better place.

As far as the show goes, early on they said, "All right, so we are going to run from this spot to another." And they realized that I was not going to do that. Not only could I physically not do that, but I was very adamant about just saying no. It was up to me to make sure that I was vocal about what I can and cannot do and things were adapted. I have nothing bad to say as everybody on the crew and the producers at Top Chef were all about trying to make sure I was comfortable. During Restaurant Wars, they offered me a stool to sit on, but I refused to do it because I wanted to compete as closely as possible to how all the other chefs were competing. I wanted to make sure that I was not given any sort of real special advantage, such as more time or anything like that. I was going to do this on my own. I think that the mental and physical preparation that went along with that, whether it was stretching or getting rest before and after challenges, was really important for me. There was one time where I fell asleep in a folding chair as I was so exhausted. My body said, "You must go to sleep," and completely shut down. Sometimes you have to listen to your body and know what you need.

Erika Berg (*host*):
I would now like to talk about the workplace and what we share with our coworkers and the world. Managing workplace relationships can be challenging for everyone and with a disability it becomes even more challenging. Bonnie, how do you decide what you want to share with coworkers about your condition?

> ***"It is sometimes a surprise to people when I do disclose and I am still shocked by people's responses. I do not know if I will ever get used to the responses that I get. So I think there are days where I simply do not have the emotional energy to manage other people's responses."***

Bonnielin Swenor:
That is a great question. I will first say that I can easily hide my disability. So I have the privilege and the disadvantage, in some ways, of being able to choose what I want to disclose, or not, in many situations. Not in all situations anymore, but in many. I say that because it is oftentimes a privilege to hide it, but it can also be a painful conversation to have, and can come with a lot of pushback when I do disclose. How do I make that decision? Usually it depends on if it is pertinent to what is being discussed, which oftentimes, because of my work, it is. If I think it is going to be helpful to the conversation or the relationship I usually disclose. Usually with students, I am very upfront about it. To be honest, I think at this point, my disability precedes me for better or worse, and usually for the better.

However, there are many occasions when I do not want to have the full-on conversation. I do not feel like answering all the questions that I am going to get. Honestly, in the workplace, it has gotten better, probably because this is my career. It is actually in personal spaces where it is more difficult. For example, as a mom on the playground, I do not want to have that conversation with other moms, every time. It is sometimes a surprise to people when I do disclose and I am still shocked by people's responses. I do not know if I will ever get used to the responses that I get. So I think there are days where I simply do not have the emotional energy to manage other people's responses.

Ashley Shew:
It is too many things to disclose sometimes. I am multiply disabled from chemotherapy. I am a hard-of-hearing, chemo-brained amputee with tinnitus and Crohn's disease. But I am not going to tell people all of that. I think it explains why I ask for particular things. I have also tried to make sure that my advocacy involves things like asking why the elevators are locked every back-to-school night. They know for sure that this event is open to the public. There will be disabled people present. I just want to use the elevator so I can access the same places everyone else can. Everyone else gets to go with their kids happily in all these spaces. Instead, I am watching people in knee braces on the stairs when we have the technology available. It is not even asking them to pay money. I am asking them to flip a switch. I feel like there are so many areas where we actually have things set up in ways that could make spaces more accessible.

I think about Dan having his own kitchen. He can set it up in ways that work for him. We are lucky when we get into positions of power and can control these everyday things that let people see that we can do a good job, when we can use basic technology that has been established for many years. The constant advocacy is ridiculous, and when I have the energy, I am going to advocate for someone else's disability as well. Because I know that we do not all have the energy. We have to pass the baton regularly in order for any of us to survive.

> ***"I think I have proven and they can tell that my relationship with having a disability makes me more motivated in lab. They know that I will do my work well and sometimes even better than my peers who do not have that same motivation."***

Elizabeth Caldwell:
I think in terms of disclosing my disability in my role as an undergraduate researcher, I have thankfully been in spaces where I felt comfortable enough to be very honest with my principal investigators about what I think I can or cannot do. They have all been very understanding. I think I have proven and they can tell that my relationship with having a disability makes me more motivated in lab. They know that I will do my work well and sometimes even better than my peers who do not have that same motivation. I think the difference comes in when you are disclosing to people that you are not going to have an extended relationship with. I think that is what confuses me. When I first came to school with my cane, in every single classroom I entered, I had at least one person ask me why I used the cane. The questions ranged from, "Are you okay?" or "Why are you using a cane?" to more direct ones like, "What's wrong with you?" I love to advocate, but when I cannot even be a normal student and focus in class or when I go to the grocery store, and keep having to answer the question of what exactly is wrong with me, that is where disclosure gets a little awkward. I am just trying to be a normal person and I do not understand why we have normalized asking strangers about their health history, or assuming it is an injury. I am proud of my disability, so I do not try to hide it. What I cannot stand is when I say, "I am actually just disabled," and it is as if I just said I had the plague. Then the person who was sitting next to me in my class, who was a stranger, wants to keep themselves a stranger, because they feel like they just uncovered this landmine. They pull back and they never speak to me again. That is where the biggest problems occur.

Dan Jacobs:
That is sad, but I think I have had similar interactions. What I did on Top Chef was very public and I made that decision. However, people will come up to me and ask me, "How are you doing?" That is always the most loaded question I think somebody could ask me. It is a deeply nuanced question and I do not even know you. So most of the time I say I am fine. But I did the show

because I wanted people to be inspired and to realize that we can do more than people think we can. It is something that we somehow learn to deal with, but you are absolutely correct about the stigma. When I tell people I have a rare neuromuscular disease, there is almost a pull away sort of situation where I have felt that same thing, and where I almost feel like saying, "I am not going to sneeze on you, you are not going to catch it." I am sorry that this is happening to you Elizabeth. School should be fun, or at least a little bit.

Erika Berg (*host*):
Thank you for sharing those stories. I would like to shift gears a little and talk about some strategies for success. Elizabeth, what strategies have helped you navigate the lab environment with a disability?

> ***"Seeing two people in a lab who both live with a disability is really empowering. We are both extremely productive, we have a positive attitude about it and we make great strides in what we do because we are both motivated by our own condition."***

Elizabeth Caldwell:
I think first and foremost, the most important thing for me is feeling socially accepted by my principal investigator and my lab mates, because when you feel like you are on a team, it becomes a lot easier to be yourself and advocate for your needs. As I said before, my principal investigators have both been very understanding, and they know my backstory and what I can or cannot do, but it is based on what I say. They do not assume I cannot do certain assays just because I have a disability. I think that is the most important thing: having an employer, a boss, or a principal investigator who will let you tell them what you need rather than making an assumption about what you need.

Having an inclusive lab space is extremely important to me. All of my closest friends are actually in my lab back at Clemson and I made amazing friends at St. Jude as well. They are extremely helpful when I do need an extra hand. Sometimes, when I have a flare-up, I have trouble opening a tube, but I do not feel like I am a burden for asking for help. And having trouble opening a tube does not mean I am not mentally capable of conducting meaningful research. I just need help with the tube. I actually have several lab mates at Clemson who also have disabilities and one of them actually has the exact same condition as I do. Seeing two people in a lab who both live with a disability is really empowering. We are both extremely productive, we have a positive attitude about it and we make great strides in what we do because we are both motivated by our own condition. But that is all to say that the physical lab is not necessarily accessible. When I need to use my wheelchair, I cannot be at the bench with my wheelchair and have to transition to a high-top. Thankfully, I have the physical ability to do that, but I think labs have been designed without inclusivity in mind. I think that is because of the unconscious bias we have that people with disabilities are not going to do basic science research. All of the doors are too heavy and none of the benches would accommodate a wheelchair. There are simply things in the lab that are not accessible. I am not going around and demanding every single lab become the most physically accessible for me, I just think it would be nice if we could start having that in mind when we design spaces for these careers. Because it is almost a subconscious assumption of, "We do not expect you to be in this career, so we will not design it for you." When you want to go into a career, and you look at all these spaces, why would you want to enter into a space that is not made for you? I think that further excludes people with disabilities from STEM and basic science research, because they can see that it is so inaccessible. I think if we can start redesigning things, and once again, my biggest catchphrase is: do not assume anything about us, we will see real change. So many people are inspired by their condition, their rare disease or their disability, and they want to do that research. They want to fill that gap themselves. Patient scientists are needed. We just need to create a space where they can actually do that, and then I think we will surprise everyone with how much work we can actually do.

Erika Berg (*host*):
Bonnie, are these types of issues, like making science STEM careers and lab spaces more accessible, being discussed?

Bonnielin Swenor:
We certainly need more discussion, but I would say in the past few years there has been some policy change and conversation in some high levels of federal science policy about the prioritization and the need to prioritize making STEM more inclusive for people with disabilities. That includes the second "M" in STEM, which is sometimes expanded to STEMM, for medicine. This includes the universal design of spaces and places, communication, information, and also addressing the ableism that is often present in STEM. As a scientist that uses data, we need more data to help drive that change. That is also a part of the conversations that are being had so that we know where and when things are working and when they are not. We do not even have that yet. So there is lots of work to do, but progress is happening at a faster pace than ever in my career, which is a good sign.

Erika Berg (*host*):
Sounds like there will be a young army of patient scientists just waiting for this opportunity. Ashley, I was wondering, with your personal experience in academia, and with your teaching responsibilities, if you can talk about your experience and how you have navigated your workspaces and what accommodations and strategies have been helpful for you.

Ashley Shew:
I think this is true for many people, but the official channels are often not very helpful. I work with many other disabled people and my research groups end up being majority disabled spaces, just by happenstance. Usually most of the teams I am on include other disabled people. Now that I sometimes lead projects, it is not that

I exclude non-disabled people, but the people who are drawn into the type of research I do are often disabled as well. So I actually hear a lot of stories from other people who are trying to navigate a particular infrastructure. At universities, things are really hard for students who are also researchers. Students have to go through services for students with disabilities. It is called many things, but it is a student office for classroom accommodations. Then, there is a second office for workplace accommodations that faculty and staff use, that often students have not even been told about. Services for students with disabilities only cover classroom and some campus stuff, but they will also refer you out to residence life. So it involves twice the paperwork. Those offices have not talked to each other in decades. It is different paperwork and what they can actually offer at the end of the day that might help is really kind of silly. We therefore go through all of this work to get accommodated and to be included. We need accommodations to be included. These may include a workbench you can work at or, for one of my friends with migraines, a different shade of light bulb and not fluorescent lights. It is usually not very complicated things and people have to fight tooth and nail to get them. Most accommodations cost employers under $500 over the course of the life of the technology we are talking about. It is not like accommodations cost the university that much, yet they still get policed. I am lucky in that my physical disability is a very visible one. So in disability spaces, people can infer why I might be there.

"At some universities, if you are teaching, you have to resubmit paperwork every semester, even though some of our disabilities do not change that much or at all. So it just seems like a never-ending stream of paperwork, which I feel is one of the biggest hurdles of being disabled."

At one point, we had to shift my teaching online. My university dropped its mask mandate and my classroom was an enclosed space. We had to run really heavy duty air purifiers in the room and I am hard of hearing. My hearing aids really love buzzing sounds and amplify them. So I was just listening to buzzing and my students were talking and I thought, "What is this new hellscape that has been created for me?" Because of this, we actually shifted my class online, but I had to submit recent audiograms to show my level of hearing loss, which I did not think was really relevant. The fact that I use hearing aids was relevant. They do not know what I hear and what the hearing aids are causing to be amplified. I would have liked to have a discussion-based class. They were making it really hard to do so. I shifted online for that one, but I was basically warned that I could not keep asking for online teaching because our provost was pressuring everyone to be in person all the time. They said that they would make this a one-time exception. At some universities, if you are teaching, you have to resubmit paperwork every semester, even though some of our disabilities do not change that much or at all. So it just seems like a never-ending stream of paperwork, which I feel is one of the biggest hurdles of being disabled. That does not even include all the insurance paperwork we have to do. Sometimes people hand me a form for something and I just want to start swearing. It is not at them personally, but none of it needs to be this hard. It is set up in a hostile way because they do not want disabled people there. They want to police us out of spaces. We have to remember that our institutions are ableist. Jay Dolmage has a wonderful book on academic ableism that talks about the history behind it. When we talk about sciences and research in universities, much of it was justified as a way to understand, characterize and segregate people. If we are talking about the era of eugenics and institutionalization, it was always non-disabled people talking about disabled people as objects that needed to be managed or eliminated. In fact, the Americans with Disabilities Act does not specify any specific paperwork you need to complete to get accommodations. It does not say you need a note from your doctor. That is how it has been interpreted in ways that are hostile to disabled people.

Erika Berg (*host*):

Let us now switch gears to the kitchen, which is not that different from a lab. Dan, how have you adapted and prepared that space, especially given the physical demands? And what advice would you give to young chefs with disabilities about creating accessible and supportive spaces?

Dan Jacobs:

Elizabeth touched on this, but I think the biggest thing is having the conversation and bringing the team along with you by explaining to them what you are going through and what you might need. It sounds really simple, but it is harder than it seems. I am an optimist (I am a lifelong Cubs fan), so I believe people want be good and do the right thing. It is so important to have that conversation with people when you need help. Elizabeth, I really relate to what you said about opening jars. I am constantly asking, "Hey, can you open this for me?"

I think people understand that and they want to help. Some of the things that we have done to make the kitchen a little more accessible include doubling down on slip-resistant surfaces. I fall really easily all on my own and do not need any extra help. So we make it as safe as possible. Having areas where people can work sitting down is also important, because sometimes my legs are just so tired that I need to have a stool or an area where I can sit and prep at the same time. I think the biggest one is having that interaction with people and talking to them about what you are going through. Restaurants are unique places as you have creatives and people who are in it for the love of the game. That makes them special places, where people tend to be a bit more empathetic.

Erika Berg (*host*):

Bonnie, you have been involved in translating research data into policy change. Can you share some examples of how data is being used to drive more inclusive workplace practices or policies for people with disabilities? How are we using that data to help?

"Data is an important lever for change, and it has not been used for people with disabilities enough. We do not have the data infrastructures like we do for other groups that are often excluded, and without data, it is almost as if we do not count."

Bonnielin Swenor:
Well, we certainly need to be doing it more often. I would like to share a story. After the experience I talked about earlier, where I was kicked off the team, it was a pretty low point for me, and I had to grapple with my biggest fear: that people would not want to work with me because of my disability. I was worried I was going to be pushed out of my career. So I did the only thing I knew how to do, which was research. I wanted to find data on how many people with disabilities were working in this field, but despite an extensive search, I could not find anything. Eventually, I filed for a Freedom of Information Act request to get data on people with disabilities who have received funding from the National Institutes of Health (NIH). And as a cathartic act, I published that data. What I learned from that experience was that people pay attention to data. I received some responses and that data, along with other's data, led to several changes in committees, which have brought about ongoing change at the NIH and elsewhere. It really showed me how we need both people's stories as well as quantitative data to demonstrate that including people with disabilities is a priority and is necessary. Like I said before, the data we need is where and when it is working and where and when it is not. Data is an important lever for change, and it has not been used for people with disabilities enough. We do not have the data infrastructures like we do for other groups that are often excluded, and without data, it is almost as if we do not count. We are not included in policies or evidence-based decision-making. That is why it is so important to focus on data. As researchers, we can embrace our love of data to drive change.

Erika Berg (*host*):
Elizabeth, what advocacy issue stands out for you or what is the top priority in your mind for making workplaces more inclusive?

""Nothing about us without us." I think if you let us in the room where decisions are made, we can really inform things. This is something that I am constantly trying to prove: that my experience is invaluable in a lot of spaces, whether it be research, policy, or patient care."

Elizabeth Caldwell:
That is a very big question. I think that there are a lot of things that can be done, but the phrase that has been published everywhere for a lot of different minorities is "Nothing about us without us." I think if you let us in the room where decisions are made, we can really inform things. This is something that I am constantly trying to prove: that my experience is invaluable in a lot of spaces, whether it be research, policy, or patient care. While I do have a disability and it does give me challenges, I think I have an advantage in those experiences as I have actually lived them. I am an expert in that field. It is literally in my genetics, since I have that disability. So if you give us a seat at the table, we can really start making changes that will improve the lives of most people with disabilities. Thankfully, Clemson has given me that space and allowed me to try to make some of those changes, but we need to continue doing that. It should not take a disabled person's motivation to be included. I think institutions should want to do that before someone individually comes and says, "Hey, I want to talk about this. Put me in the conversation, please. I am not being included. I am not being heard." I think taking that initiative, before someone has to experience discrimination to bring it up, would be a good change.

Ashley Shew:
I think it is really important to recognize expertise and to view disabled people as experts with their lived experience of disability, especially in community with one another. I would love to see a world where people believed disabled people without requiring us to justify ourselves or provide a lot of health information, especially in the world of rare diseases. You do not always know how things will unfold. Asking for extra paperwork that explains what is going to happen in the future is not always possible and creates an undue burden in the workplace.

Erika Berg (*host*):
Dan, you have been an advocate for Kennedy's disease. What do you think are the biggest issues? How can professionals with rare diseases use their platforms to advocate for their communities?

Dan Jacobs:
I think I am going to echo a lot of what has already been said. However, I think being in the room to inform the decision makers is really the most important thing. It is also important to realize that your government works for you, and that you work for your workplace. In general, I think people want do the right thing, and I am hoping that, given the opportunity, we can make a lasting change that will allow us all to feel comfortable in our spaces.

"Including us is not a nice thing to do, it improves the work we do. And that is the shift that I think really needs to happen."

Bonnielin Swenor:
I would just add that I think there has to be this mindset shift. Including us is not a nice thing to do, it improves the work we do. And that is the shift that I think really needs to happen.

Bright breakthroughs: Real stories of beating rare disease

What is the ultimate example of a win in rare disease? A cure. While a lot of attention has been focused on emerging cell and gene therapies, there are other promising roads to a cure as well, such as repurposed drugs. Many obstacles still exist as the science evolves and access issues remain, but there are a few shining examples of what these new technologies could mean for people living with rare disease.

In this webinar, participants will

- Learn about the latest research in curative treatments for rare disease
- Hear about first-hand experiences with cures for rare disease
- Explore what the future holds for these treatment modalities and what they mean for people with rare disease

Panelists

Bill Hobbs, M.D., Ph.D.
Vertex Pharmaceuticals, Boston, MA

Michelle Werner, BA, MBA.
Alltrna, Cambridge, MA

David Fajgenbaum, M.D., MBA, M.Sc.
University of Pennsylvania, Philadelphia, PA

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

The Conversation

Erika Berg (*host*):
While a lot of attention has been focused on emerging cell and gene therapies, there are also other promising roads to a cure, such as repurposed drugs. But many obstacles still exist, the science continues to evolve and there is also the issue of healthcare access. However, there are a few shining examples of how recent advancements are bringing actual cures to people living with a rare disease. I would now like to take the opportunity to welcome our fantastic panel today.

Michelle Werner:
I am the CEO of a flagship pioneering company called Alltrna. We were founded in 2018. We are still preclinical right now, but we are really focused on unlocking the biology of tRNA, or transfer RNA, to treat a number of different rare genetic diseases. One of the cool things about our technology is that we can use a single one of our medicines to treat hundreds, if not thousands of different diseases. When you have rare and ultra rare diseases, you can clearly appreciate the potential impact that this might have on bringing new innovation to a lot of patients who may not otherwise have that. So, that is what I do in my day job. I would say the other part about myself and my connection to today's topic is that I am a wife and a mom of three kids. One of my children is 14 years old. His name is Caffrey and about four and a half years ago, on his 10th birthday, he was diagnosed with Duchenne muscular dystrophy, which is a rare genetic muscle wasting disease that is progressive in nature. Today, there is no cure. So, I have been thrust into the rare disease community myself and am really passionate about bringing novel innovations to patients and families that are pretty similar to my own. It is a pleasure to be here and happy to talk about our story, both personally and professionally.

Bill Hobbs:
I lead the clinical development programs for hematology at a company called Vertex Pharmaceuticals. The area in particular that I have worked on for a number of years is in sickle cell disease and beta-thalassemia. We have recently developed a potential treatment called exa-cel, a CRISPR-Cas9 gene editing program for the treatment of transfusion-dependent thalassemia patients and severe sickle cell disease with recurrent vaso-occlusive crises, which is now known as Casgevy. I have now been involved in hematology and in sickle cell disease for well over 20 years. I originally started from a research standpoint, being interested in being able to leverage technology to develop genetic therapies for diseases. For a long time, sickle cell disease and beta-thalassemia had been model diseases, with everyone believing that, at some point, we would be able to develop a genetic therapy for them. However, it took a very long time to get there. I think what changed as I was developing my career was moving from a scientific focus into one that was more patient

focused. In my case, that happened with the exposure to people living with sickle cell disease and beta-thalassemia in medical school. That changed everything and I think that is a common theme for people that get involved in rare disease. It is really the patients and families who are affected that drive all of us. What becomes very clear in that setting is how difficult it is for people to get equitable access to appropriate care. The research resources are sometimes limited and the treatment options are as well. The motivation for me along the way has been to merge that research interest to develop tools that can become treatment options for patients who really have very few, if any, other options. That was certainly the case for sickle cell disease and beta-thalassemia. So, for us at Vertex, this has been a very rewarding journey in terms of developing what could be a treatment option for patients who have a severe and life-limiting disease with very few other options.

David Fajgenbaum:
My name is David Fajgenbaum. I run a center at the University of Pennsylvania called the Center for Cytokine Storm Treatment & Laboratory, where we do in-depth immune profiling of rare inflammatory diseases. I first got exposure to rare inflammatory diseases when I was a medical student here at Penn, and I became very ill with a rare inflammatory disease called Castleman disease. I nearly died five times from this horrible condition before eventually discovering a drug called sirolimus that had been around for decades for other diseases, but had never been used for this disease. I tested it on myself and it has now been over 10 years that I have been in remission. During this 10-year remission, I have been completely on fire trying to find as many more uses for existing medicines as possible. Here in our lab, we have identified over a dozen additional drugs for diseases that they were not initially intended for. Then, two years ago, I launched a nonprofit called Every Cure to do this at scale, by leveraging the power of artificial intelligence to scan the world's biomedical knowledge, across every drug, disease, gene, target, and protein imaginable. Our goal is to quantify the likelihood of any of the 4,000 drugs to be able to treat all 18,000 human diseases, and then take the most promising opportunities forward. I am very excited to share more about this work, which aims to try to save lives with existing medicines.

Erika Berg (*host*):
We are going to start by talking about the science. Bill, can you describe in a little more detail the journey behind the development of Casgevy?

Bill Hobbs:
The name in development is exa-cel, which is actually short for exagamglogene autotemcel. I think for a lot of rare diseases, and sickle cell disease and beta-thalassemia are like this, we have known about them and their underlying cause for a long time. Sickle cell disease was first described over a hundred years ago clinically, and the causal biology of it being a mutation in the beta-globin chain of hemoglobin has been known since the 1950s. We have also known since the 1940s that fetal hemoglobin reduces the impact of sickle cell disease in research that was published by Janet Watson in 1947. So, we have known about these things for a long time, but what changes over the years is our understanding of the biology. We gain more and more information about understanding what potential targets we could actually attack for potential treatments and what tools we could use for those.

What really changed for us at Vertex was the first description of CRISPR-Cas9 gene editing about 10 years ago, which could be potentially used as a therapeutic, meaning that you could potentially identify a precise and specific place in DNA and make a very precise edit that could alter the profile of a disease. What came shortly after that was the understanding that the regulation of expression of fetal hemoglobin was largely driven in developing red blood cells in the bone marrow by a transcription factor called BCL11A, and that BCL11A expression in those developing red cells was controlled by a very specific enhancer element in the promoter. When you put these two elements together (the development of a technology platform and the identification of a target) you can say that if you edit that site in the BCL11A erythroid-specific enhancer, you can alter the BCL11A expression in developing cells of the bone marrow and turn on fetal globin expression, which we have known since 1947 to be protective in this disease. That was really the story behind what became Casgevy: a long history of understanding the biology of the disease and then the relatively rapid development of additional molecular features and the CRISPR-Cas9 editing technology that enabled the development of a novel therapeutic. It is this really nice intersection of biology and emerging technology that rapidly translated into the clinic, which for rare diseases is something that is common to what both Michelle and David are pursuing as well.

Erika Berg (*host*):
Would you characterize Casgevy as a gene therapy?

Bill Hobbs:
It is a cellular therapy that uses a CRISPR-Cas9 gene editing approach. We take the stem cells from a patient, they are edited, and then they are returned to the patient as a cellular gene-edited product.

Erika Berg (*host*):
It is interesting you are talking about this long history and how we have known the underlying cause of sickle cell anemia for a long time. I am curious: did you gain insights into gene and cell therapies throughout your journey that could be applied more broadly?

"There has been a long history of developing novel types of therapy, including genetic medicines. What has really changed is the refinement of the technology and its specific application for a disease. That really requires an understanding of the underlying cause of the disease in order to know how to use these tools to develop a potential treatment option."

Bill Hobbs:
I originally got interested in science, research and medicine as an undergraduate student. It was serendipity because I had an opportunity to work as an undergraduate in a research lab that was directed by a very inspirational virologist who was interested in using viruses for gene therapy. I think that viral vector based therapy was the original vision for what genetic therapies could become. There have been many such developments using them and progress continues. I think the interest and vision behind this has been going on for a very long time. For me, it was in the 1980s, but there were theories and platforms that were developed in the 1970s as well. There has been a long history of developing novel types of therapy, including genetic medicines. What has really changed is the refinement of the technology and its specific application for a disease. That really requires an understanding of the underlying cause of the disease in order to know how to use these tools to develop a potential treatment option.

Erika Berg (*host*):
David, the medications that you are looking at are already out there in the world. We just do not necessarily know what they do. Can you talk about how you are trying to unlock the potential of these drugs through your technologies at Every Cure and have you discovered anything surprising in the process?

> ***"... there are still 14,000 diseases without a single approved therapy."***

David Fajgenbaum:
There are about 4,000 FDA approved drugs, which we as humanity should be so proud of. It is incredible: 4,000 drugs approved for about 4,000 diseases! However, there are still 14,000 diseases without a single approved therapy. The amazing work being done needs to continue to develop new drugs for many of those 14,000 diseases that do not have any therapies. The good news is that many of those 4,000 existing drugs could potentially treat some or many of these diseases that do not have any treatments. You mentioned that we are looking for drugs with unknown potential uses, and that is the case. We are looking to identify new uses for drugs that the world does not know about, but what has been really surprising is that we found a lot of additional uses for approved drugs that the world already knows about. The challenge is that there is some sort of systemic barrier that is preventing that drug from reaching patients. Usually it is because the drug is cheap, old, and generic, so there is no path forward to market the drug or to commercialize it in a new disease area. That, I think, has probably been the biggest surprise, and I will share a couple of examples. One of them is the use of TNF inhibitors for a rare disease called deficiency of adenosine deaminase 2 (DADA2). DADA2 is a horrible condition where kids start having strokes soon after birth, and they usually die in their teenage years because they have hundreds of strokes. About 20 years ago, a physician decided to try a TNF inhibitor in one of his DADA2 patients. It was actually because he had leftover TNF inhibitor in his syringe. He just treated one patient, and he decided to treat another patient, and then that patient stopped having strokes. Over the course of the next few years, he saw more DADA2 patients, gave them TNF inhibitors, and they did not have strokes either. It was 15 years from that initial observation before the DADA2 Foundation, led by Chip Chambers, began to put data together around this. Chip then came to us and we started putting together treatment guidelines, so that everyone with DADA2 syndrome could be recommended to actually get a TNF inhibitor. Now, 20 years later, every child with DADA2 is receiving a TNF inhibitor. However, because there was no commercial path forward and because TNF inhibitors were being utilized for more common diseases, as opposed to a rare disease like DADA2, 20 years passed and thousands of kids died from strokes, despite knowing there was an effective treatment available. That is a really extreme example, but there are many more like that.

> ***"We are looking to identify new uses for drugs that the world does not know about, but what has been really surprising is that we found a lot of additional uses for approved drugs that the world already knows about. The challenge is that there is some sort of systemic barrier that is preventing that drug from reaching patients. Usually it is because the drug is cheap, old, and generic, so there is no path forward to market the drug or to commercialize it in a new disease area."***

One that we have come across recently, and that scored really well on our platform, is a drug called leucovorin for a rare percentage of children who have autism. In these children, we say that they have autism spectrum disorder, but they actually have antibodies against the folate receptor, resulting in folate being blocked from reaching their brain. We call it autism spectrum disorder, but it is actually a cerebral folate deficiency. If you give them high dose leucovorin, which is a reduced form of folate, it can enter the brain through a folate transporter. There have been four randomized controlled trials showing that leucovorin can improve speech, verbal communication, and a number of other ASD-related symptoms in these kids, but no one is receiving it. This is because leucovorin is cheap and old and has been around for decades. So these are drugs that are literally hiding in plain sight. In these couple of cases I mentioned, we did not have to do any clinical trials at Every Cure. We literally just had to use our platform to uncover them. At Every Cure, we are using this platform to quantify the likelihood of every drug to treat every disease. Sometimes they are predictions, like you mentioned, but sometimes we are just uncovering work that someone else started, but did not take to the finish line. So, we do lab work and clinical trials and, in some cases (such as with leucovorin), we put spotlights on these opportunities and really encourage the off-label use of these medicines.

Erika Berg (*host*):

Can you explain, in a nutshell, how your platform works?

David Fajgenbaum:

Of course. We utilize what are called biomedical knowledge graphs. We have a handful of knowledge graphs that we use, which are visual representations of what the world knows about all of human biology and all of medicine. You can imagine that these different graphs contain between three and ten million nodes. A node in a graph is a biomedical concept that is then connected by edges. For example, Castleman disease is a node and it has an edge to interleukin-6 (IL-6), because Castleman disease is associated with increased IL-6. IL-6 has an edge to siltuximab, because siltuximab inhibits IL-6. So now you have a triplet between Castleman disease, IL-6 and siltuximab.

Now imagine doing that across all of human biology and all of human knowledge, with somewhere around 5 million nodes (depending on your graph), and tens of millions of edges connecting each of these concepts. We now have a sort of 2D representation of what the world knows about human biology and all of medicine. We then train algorithms on known treats relationships, meaning examples like siltuximab for Castleman disease. We train the algorithm on examples where the drug works for this disease. We also train the algorithm on examples where the drug does not work for this disease. Then we unleash the algorithm on the rest of the knowledge graph to come up with a score from zero to one. We use an algorithm called XGBoost, and if the pattern of connections in a new drug-disease connection, such as folinic acid for pancreatic cancer, resembles a known treatment relationship, the score will be high. If it does not match, the score will be closer to zero. Then, our team at Every Cure looks at the highest scores and says, this drug for this disease looks really promising and we do the laboratory work and clinical trials so that we can move them forward.

Erika Berg (*host*):

We are now going to move on to tRNA. Michelle, can you tell me a little bit about tRNA and how one approach could have large ramifications and potentially treat many diseases? Could you explain how it works and why it could be considered so semi-universal?

Michelle Werner:

I will start by talking about what a tRNA is and then we can go into why it is important and how we think it can be used. The tRNA plays a critical role in the protein translation process. I am sure everyone has heard about the central dogma of how DNA codes for an mRNA, which codes for all the amino acids that make up a protein. On the mRNA, each amino acid is encoded by a three-letter sequence that makes up each and every amino acid and the chain of amino acids forms the proteins, which keep us healthy and alive. The tRNA plays this critical role where it actually deciphers the code for each and every amino acid on that mRNA coding sequence and then finds that corresponding amino acid in the surrounding cellular environment and transfers the amino acid to the growing polypeptide chain. That is why it is called "transfer RNA", because it plays this important transferring role of the amino acids.

"Now, of course, when you have somewhere between 6,000 and 14,000 of these different diseases, and we are trying to tackle them one at a time, it is going take an eternity before we make a dent in them. Often, the way that drug development works is you start in one disease, you prove that it works and then you start in the next one and it is this sequential iterative process. We are taking a much broader approach by identifying patients that have common mutations across all of those different diseases."

Now, what happens when you have different diseases? David, you were the first person that actually mentioned 14,000 different diseases. I have always said somewhere between 6,000 and 10,000, but I think that is part of the issues. I do not know if anybody is completely sure of how many discrete diseases there are, but it is a lot, and over 80% of these diseases have a genetic component to them. When you consider all of the modern technology we have access to today, including small molecules, genetic medicine (like gene therapy, gene editing, and mRNA-based approaches) and cellular therapies, each one requires a disease-by-disease or gene-by-gene type of strategy. This is because they are very specific to a certain gene or a certain protein and that is how those mechanisms work. Now, of course, when you have somewhere between 6,000 and 14,000 of these different diseases, and we are trying to tackle them one at a time, it is going take an eternity before we make a dent in them. Often, the way that drug development works is you start in one disease, you prove that it works and then you start in the next one and it is this sequential iterative process. We are taking a much broader approach by identifying patients that have common mutations across all of those different diseases. We start by first tackling what is called a premature termination codon or a nonsense mutation. That is where one of the codes for an amino acid gets mutated and instead codes for a premature stop, resulting in the translation process ending too early and giving you a shortened, dysfunctional or non-functional protein, which causes disease. The same exact premature termination codon mutations are seen in thousands of different diseases. We are looking at engineering tRNAs that have the ability to read through these premature termination codons, so instead of the protein translation stopping at that mutation, it actually knows what amino acid should have been coded for, finds that amino acid, restores the protein translation process and continues to the point where you have a full length functional protein at the end of the day. Because we see the same exact mutations across many different diseases, we can use the exact same engineered tRNA across dozens, hundreds, or perhaps even more different diseases because we are taking a very mutation-specific approach, not a disease-specific approach. In fact, it is actually disease agnostic. So, natural tRNAs and our engineered tRNAs both perform the same function. The biology is exactly the same regardless of the gene that is affected, regardless of the protein that is being encoded. It

also works regardless of where the mutation occurs in the coding sequence, which again, is one of the unique features about this type of technology. What is really exciting is the way that we are thinking about developing these medicines. It is not just the typical one clinical trial with one disease and one medicine. We can do one clinical trial with one medicine, but for multiple diseases, with patients selected by those common mutations. What that allows is not only having a clinical trial or an intervention available for perhaps the most common of these genetic diseases, but we can also bring along all of the ultra-rare, or maybe nano-rare type diseases, that may be a part of the 14,000, and are often are too small to be addressed individually. They just do not fit the model for a disease-by-disease strategy and will, unfortunately likely never have a novel dedicated innovation. This may allow the opportunity to bring along all those patients with a mutation specific strategy, independent of disease, and hopefully be able to offer some optimism and hope for those populations.

I can speak to how important that is for families. When my son was diagnosed a number of years ago, especially as somebody who has been in the industry for a couple of decades, the first thing I did was start to explore what clinical trials were ongoing that he might be eligible for. I was really horrified when I realized that there were zero interventional clinical trials that he was eligible for. My heart just sank at the possibility of him being one of these overlooked individuals that will never have anything other than a standard of care that has not changed for several decades and is really not acceptable. So, I know what it is like to be one of those families and I hope that with this type of technology that we are developing here at Alltrna, that other families like ours will not have to experience that same type of feeling.

Erika Berg (*host*):

Is the actual therapeutic agent like the tRNA? So is it a small molecule type drug approach or is it a gene therapy?

Michelle Werner:

It is an oligonucleotide, which is an RNA-based technology. I would put it into a genetic medicine category. It not a small molecule, but it is also not a gene therapy. I guess it fits into this own category and it is its own new class of therapeutics.

Erika Berg (*host*):

You are all doing different and amazing things that are having a real impact and bringing a lot of hope. Bill, are there benefits to be gained from having many different strategies and approaches when tackling rare diseases?

"I think what is really exciting right now in the space is that there are so many different technologies that are now emerging and available that we can use to help people living with rare diseases."

Bill Hobbs:

I think that is a great question and what is exciting, particularly now for a lot of rare diseases, is that the technology options that we have available to us are exponentially increasing. Ten years ago, we did not have CRISPR-Cas9 gene editing. The technology that Michelle is referring to is also newly being applied. At Vertex, what we do is look for diseases that are severe, life-limiting, life-threatening, and that we have an understanding of their causal biology, meaning that there is a validated target that we think relates to clinical outcomes. The example is in sickle cell disease, where we understood that the BCL11A erythroid-specific enhancer target could increase fetal hemoglobin, which, based on over 50 years of natural history clinical research, is known to protect against disease complications. If you then take the next step of what is needed to address that target, it could be any number of different tools. For us, it ended up being CRISPR-Cas9 gene editing for sickle cell disease, but for another disease, that may not be the right technological approach, and it could be something very different, such as tRNA, a small molecule, a biologic or any number of other therapeutic modalities.

At Vertex, our approach is really to take whatever tool is best suited to target the biology and achieve the desired outcome. I think at large, every disease, and particularly those in the rare disease space, can be a little bit different and may need a different approach to hit the underlying biology. That is probably the most platform-agnostic way to think about it. There will be common types of approaches where one platform makes a lot of sense for a lot of different diseases, but for some, that may not be the right approach.

I think what is really exciting right now in the space is that there are so many different technologies that are now emerging and available that we can use to help people living with rare diseases.

"With 14,000 different diseases, you can imagine the diversity amongst them is massive, so there is never going be one single way in which all of those different diseases can be tackled. "

Michelle Werner:

With 14,000 different diseases, you can imagine the diversity amongst them is massive, so there is never going be one single way in which all of those different diseases can be tackled. I do think that the responsibility is on us, as scientists and curious individuals aiming to push the understanding forward, to really explore many different options so that patients have as many shots on goal as possible.

"You have this world where someone is suffering, and then there is this drug that is actually at their neighborhood pharmacy that could help them, but the world is not making the connections."

David Fajgenbaum:
I completely agree. I hate to say this, but it is actually 18,000 diseases. It is just 14,000 that do not have treatments, so we have 4,000 out of 18,000 figured out. I totally agree with both Michelle and Bill, and I think that we need to be taking as many shots on goal as possible, and on top of that, we need to recognize that for drugs that have already been developed and they are on the market, as Michelle said, there is this sequential, "We found a disease for it, let us find another indication", but we know that as soon as that drug begins to get close to patent exclusivity or is losing patent exclusivity, then all research stops. So even when we make the new discovery that graft-versus-host disease (GVHD) involves interleukin-6 signaling, if that interleukin-6 inhibitor, tocilizumab, is towards the end of its life cycle, the work is not going to be done to then look at tocilizumab for GVHD, for example. So there are a lot of these opportunities where there is a really good mechanism, but the incentives are not there. You have this world where someone is suffering, and then there is this drug that is actually at their neighborhood pharmacy that could help them, but the world is not making the connections.

We need very disease-specific work, but then we also need these disease agnostic approaches, and we describe what Every Cure is doing as being disease and drug agnostic. We do not have any drugs in our pipelines, we do not care what the drug is, and we do not have any diseases that we are focused on. We do not care what the disease is, as we just want to help people. If you can quantify the best connections between every drug and every disease, without focusing on one disease or one particular group of people, as your primary goal is helping people, then all of a sudden, these hidden cures just begin to emerge, and it is so fun!

Erika Berg (*host*):
We have been focusing a lot on rare diseases, and some of you are looking at disease agnostic approaches, so not necessarily only rare diseases, but I am wondering is there anything different about research in rare diseases that has led you down your particular research journeys, and/or challenges that are particular to rare disease communities that you are trying to address through your approaches? Let us start with Michelle.

Michelle Werner:
I think that at Alltrna, with our focus on the tRNA space, we really stand on the shoulders of giants. In the last couple of years, having learned so much from the advancements that have been made in RNA biology and RNA therapeutics across the board, with the emergence of siRNAs and mRNAs, we really have a much better understanding about how to leverage this biology and really capitalize on the biology and turn it into a therapeutic, which has been a great inspiration for us. Rare diseases are very different than common diseases. You pick up on some of the challenges, and these are not easy spaces to enter. You think about the diversity of these different diseases, many of these diseases that we have been talking about are not well-characterized or well-understood. Bill mentioned about a deep understanding of the biology of sickle cell and beta-thalassemia leading to some of the innovations in that space and then we have all of the AI work that David is doing to really understand the key issues within those discrete diseases. It really takes a fundamental understanding of the issues to be able to think about the problem and the solutions.

Many of these diseases, or even most of these diseases, are not well-characterized and even within those diseases, there is a tremendous amount of diversity between the phenotypes of patients, making it very difficult to have a universal understanding on how to tackle them. I think that is one of the key challenges that has hindered advancements within this space, not to mention the smaller patient populations which have made things a bit more difficult from a drug development perspective and then less attention from a drug discovery perspective. That is why some of these technologies that we are talking about today are so critical, because they help alleviate or address some of those challenges without becoming a limitation to future advancements.

"So, for rare diseases, I think those three aspects of research, clinical care and new therapies is what makes it really compelling because at the end of the day, it is really about helping people who do not have any other treatment options."

Bill Hobbs:
I think both Michelle and David have articulated this extraordinarily well, that the really compelling thing in rare diseases is that these are often ones where patients have very few if any treatment options. The burden and the unmet needs are enormous and that is extremely compelling. I think we feel as a society, that we should have a responsibility to do better. We hear it from patients and families all the time, and that drives a lot of this forward. I think there are the three key elements when it comes to rare diseases that you could call challenges or you could say are opportunities. There is the basic science research to understand the disease. There is the education and awareness and the clinical expertise that is needed to manage the disease. Often these are rare diseases where the access to a care pathway with an experienced clinician is not really available in many places. Finally, there is the will to develop new treatment options. David has articulated some of that very well, saying that there are a lot of challenges, which I think he has converted into opportunities, and that is phenomenal. So, for rare diseases, I think those three aspects of research, clinical care and new therapies is what makes it really compelling because at the end of the day, it is really about helping people who do not have any other treatment options.

Erika Berg (*host*):
David, as both a scientist and a patient, can you talk a little bit about how your personal journey has influenced your approach to developing treatments for rare disease?

"I love, appreciate and value basic science, and I also always want to be thinking about how can that basic science be translated? We do not want it to get published in a journal and then no one does anything about it."

David Fajgenbaum:
It has changed everything. If I had to focus in on a few, I think that the first one would be this tremendous sense of urgency that I had when I was trying to find a drug to save my life. Fortunately, I have been in remission for a long time, so that sense of urgency is not to find a drug for me, but to find drugs for other people who are currently in the same exact situation that I used to be in. That situation was one in which I was suffering and dying while there was a cure that could have helped me, and we just did not know it yet. So, I have this incredible sense of urgency that has not decreased at all since I found a drug for myself. It has almost even grown because we have literally helped thousands of people across about 14 diseases where we have found these repurposed drugs. It has grown as we have helped more people because it has made us realize that if we had not done this work, these people would not have received help. So, sense of urgency is one. I think another is being very focused on the impact with everything we do. I love, appreciate and value basic science, and I also always want to be thinking about how can that basic science be translated? We do not want it to get published in a journal and then no one does anything about it. Finally, I think the third one is that being a patient has helped me to think a lot about denominators.

I think that we can oftentimes get very focused on our disease, our task at hand, our company, or our project, but we sometimes forget the denominator, or all those other things that are not being tackled. I think that it is about a sense of urgency. It is about making sure we are always focused on the end point, which is drug in mouth or drug in vein, and helping the patient, and then also the denominator - all those people where maybe someone is not thinking about them.

I will just share a really quick example for the second point, and that is this idea about always translating. We had a patient come to our center with a horrible cancer called metastatic angiosarcoma and he had failed to respond to the two chemotherapies that are recommended. His doctor told him, "This is it. We are going to transfer you to hospice care. You probably have three months or so before your body is riddled with these tumors, and you are going to die." He reached out to our center and he said, "David, I heard that you guys found a drug for your disease. You repurposed something. Could there be something else for my angiosarcoma?" We did the simplest thing. We literally went to PubMed, the database of papers, and we searched "angiosarcoma treatment". We came across this paper that had been published three years earlier in PLOS ONE. This is not a particularly broadly read journal, but it was published. In that paper there were five patients with angiosarcoma where PD-L1 expression was measured, and four out of the five patients had increased PD-L1 expression. We are now three years later, in 2016, and PD-L1 expression, of course, is a tremendous biomarker for whether you will respond to a PD-1 inhibitor or not. However, three years have now passed between this paper being published and no one in the world is being treated with a PD-1 inhibitor for angiosarcoma. We thought why not test this patient, Michael, to see if he has increased PD-L1 expression. Initially, his doctor was completely against it because this drug had never been used before for his type of cancer. She said, "I am not going to test for it because I would not prescribe it." We tested him for it and the results came back blazingly positive. We got Michael on the PD-1 inhibitor for the first time ever for anyone with angiosarcoma. This past April marked eight years that he has been in remission. Last month, he walked his son down the aisle on his wedding day. Everyone was dying within a year and now it looks like about a third of people live full lives, or at least extended lives, on pembrolizumab for their angiosarcoma. I bring this up as an example of always thinking translationally. Those researchers who studied those five tumors and found four out of five of them had increased PD-L1 expression did their job. They did their science, they published it in a journal, and then they went and they started doing some other basic science work. No one was picking up this insight to then move it into a patient. We have to make sure that there is someone picking up the scraps, and making sure that these insights are not falling through the cracks. That is the value of something like a biomedical knowledge graph. As every one of those insights, every single node, and every single edge is inside this graph, and it gives us the opportunity to find those hidden gems that are literally just hiding there in plain sight.

Erika Berg (*host*):
Thank you for sharing that. Michelle, you are also a member of the rare disease community through your child. How has that been a big part of your motivation and has it shaped your particular approach with Alltrna? Is that condition part of your treatment goals?

"Most of these families, as was essentially the case with our experience, are told there is no medicine for them. They are told to go home and love their child for as much time as they possibly have with them. Many of these families refuse to take no for an answer, and I applaud them and I am inspired by them. Every single day, I think about those families and those groups who have made such a dramatic difference in pushing science and research forward in incredible ways that simply would not have happened otherwise. They are the heroes at the end of the day in all of this."

Michelle Werner:
Absolutely. I would say throughout my 20-plus-year career, I have always been a very patient-focused leader, but I do not think I really understood that as well as I did when my family was personally affected. We were those patients that certainly were hopeful for novel innovation. The thing that I think is so important to really recognize, especially in the rare disease community, is how critical

that patient voice is, and not just for understanding the disease, but also for driving the science and the momentum forward for those particular diseases. When my son was first diagnosed, the first thing I did was to reach out to the Duchenne advocacy groups. That is where I got my training to really understand the disease, understand what was important, and understand what was being explored in that space. I was really taken aback by the responsibility that they had, and that they take seriously, to not only educate the community of affected families like my own, but also educate scientists about what is important and educate and really inspire and oftentimes fuel dollars into research, specific for that disease. It is truly amazing, but it is not the only example. We see this over and over with so many different diseases, whether it is Rett syndrome or with the organic acidemias. These groups are doing the exact same thing, and honestly, it comes from a place of necessity. Most of these families, as was essentially the case with our experience, are told there is no medicine for them. They are told to go home and love their child for as much time as they possibly have with them. Many of these families refuse to take no for an answer, and I applaud them and I am inspired by them. Every single day, I think about those families and those groups who have made such a dramatic difference in pushing science and research forward in incredible ways that simply would not have happened otherwise. They are the heroes at the end of the day in all of this. Not to mention, offering up either themselves or their children to be tested to see if medicines are going to work for the future generations with that disease. So for me, I take this incredibly seriously at Alltrna and one of our company core values is patients deserve better. That really comes from hearing this narrative over and over again of just going home and loving our child for as much time as possible is not good enough. We need to be doing more, so I am inspired every day to do more and to do better on behalf of these families and these individuals who truly deserve it. Even in my role as CEO, we get contacted by patients and patient groups all the time, and every single week, I take every single call. I answer every single email myself personally. That is how important it is to just listen to their stories, be humbled and inspired by them, and to really fuel the work that we do at Alltrna with that inspiration. Then part of my job is really communicating that to the rest of the organization, so that they hear it and they sense it too, so that every single person matters, every single day matters, and that we really have to make the most of what we are doing to benefit these individuals.

Erika Berg (*host*):

Bill, you were talking earlier about what drew you to sickle cell disease in this community and that you had some interactions early in your career. Could you share more about how it helped shape your work and what success with Casgevy means for you?

Bill Hobbs:

I think the way that David and Michelle have articulated it from the patient perspective is really what drives a lot of this. Michelle made a statement earlier about often feeling like you were standing on the shoulders of giants. What we often think about is our research and clinical forebears. However, what that really means is the patients, because for many of these diseases, it is patients and families who have been advocating for a very long time, and in fact demanding that we should have better treatment options. That is exactly what I saw from my own personal experience when I was in the clinic. For sickle cell disease, there were very few treatment options, and there still are very few treatment options, although more now than there were back then. The way the disease was managed was essentially the same way that it was managed in 1910 when the disease was first described: patients have excruciating pain because of blockages in their blood vessels. I always like to make the analogy that it is like having a mini heart attack, but all over the body. The way that we would manage it is we would use a little pain medication, some IV hydration and warmth, and that is essentially the way that those events are managed today. So when you are in the clinic in this era, and the only thing you have to say to patients is to ask if they drank enough water today, it is really not what people are looking for and that is not what they will tolerate. I think we all respond to that, and patients have been demanding equitable access to care and equitable development of new therapeutics for a very long time and that was certainly true from my experience. When we get to the other end of it and we have a treatment option, we tend to develop drugs in terms of a primary endpoint. Such as for thalassemia, you no longer need some transfusions, and in sickle cell disease, you no longer have these painful vaso-occlusive events, for example.

But what does that really mean for patients and families? I think when you can see that translatability about what it means for their lives, like David described about the individual being able to walk his son down the aisle years later, this is what these outcomes mean. They are more than statistics. Ideally, they are changing the way people have the opportunity to live their lives the way they would otherwise choose to. In rare disease, I do not think the patients are asking for anything other than what is done for the rare diseases that have a treatment option. They are really just asking that we try to develop a treatment for their rare diseases as well, as the impact of those are no less relevant. So, that is what really drives a lot of it. For me, and for us at Vertex, it is about seeing what the outcome can be if you do have a new treatment option.

Erika Berg (*host*):

Let us now spend a few minutes talking about access and equity with these treatments. What do you believe is the biggest challenge with ensuring equitable access to these really promising gene therapies, cell therapies, and repurposed drugs? David, what do you believe are the biggest challenges, and how might they be overcome to get more people access to these life-changing treatments?

"... on repurposed drugs, the barrier is not cost, but rather awareness and understanding of their potential additional uses."

David Fajgenbaum:
In our camp, which is focused on repurposed drugs, the barrier is not cost, but rather awareness and understanding of their potential additional uses. We recently came across data around lidocaine as a treatment for pre-surgical excision in women with breast cancer. If you inject lidocaine directly into the tumor, a large randomized trial found that there was an improved five-year overall survival rate from a direct lidocaine injection, due to a really interesting mechanism. However, no one is injecting lidocaine into tumors right now, because there is no profitability from an extra squirt of lidocaine and therefore no advantage for anyone to market that. We just have to recognize that within our system, no one is going do it, unless someone starts raising awareness and advocating for it. I actually got an email yesterday from a surgical oncologist who said he injected lidocaine in his first patient yesterday. I think for what we do, it is all about awareness and education, because they are cheap and old drugs. I promise you that insurance companies do not turn down drugs that cost a dollar a day. They just do not. So, it has nothing to do with insurance or cost of the drug. For the vast majority of drugs, over 80% of FDA approved drugs are already generic. By definition, if there are multiple manufacturers, the cost is low. There is no problem getting those covered. The problem is interest and education and awareness, and if you can handle the interest and education, at least in the United States where the majority of our citizens are insured, then you are going to get these things paid for.

Erika Berg (*host*):
Bill, you have probably the opposite issue. Some of these emerging treatments are some of the most expensive medications in the world and there is a significant need for them. What are your thoughts on access?

> ***"We need our stakeholders to come together to ensure that patients have access to the right treatments that can potentially help them. Whether we are repurposing a drug, developing a new technology for a disease that has very few people, or addressing any other shared challenge, it is not easy to do. Moving government is a long-term type of endeavor. I think the starting point is to have society say, "This is what we expect and this is the framework that we need," and that often comes from patient advocates who are the initiators of doing that."***

Bill Hobbs:
I have a few thoughts. Obviously, I am on the clinical development side, so the access issues are a little bit outside of my direct scope. However, my observation about it is that there are a lot of different stakeholders that are necessary in order to get access for treatment options. They include government entities, insurance providers, patient advocates, physicians and the companies as well. I think the key is that we need to have frameworks where all of those stakeholders can work together. In particular, when we are talking about some of the new emerging technologies that require different paradigms, it is more important than ever because the patients we know are waiting. There are 14,000 diseases and that number boggles my mind. We need our stakeholders to come together to ensure that patients have access to the right treatments that can potentially help them. Whether we are repurposing a drug, developing a new technology for a disease that has very few people, or addressing any other shared challenge, it is not easy to do. Moving government is a long-term type of endeavor. I think the starting point is to have society say, "This is what we expect and this is the framework that we need," and that often comes from patient advocates who are the initiators of doing that.

Erika Berg (*host*):
Michelle, is there anything about how you are developing this whole platform technology that you are thinking about in terms of how will patients access it in the end? Or is there anything that you are building now with long term access in mind?

Michelle Werner: b
Yes, I think that we all need to really recognize that drug development is hard. Drug discovery is complex and manufacturing as well, and none of these things are cheap. You talk about having these different frameworks and paradigms, and I think that is one of the key considerations for us at Alltrna. We have to break free from this paradigm of a single drug for a single disease, because that is the most expensive way. So, in our platform, as we have discussed already, the idea of having single drugs across many diseases really helps tackle a lot of that. Instead of having to do drug discovery for thousands of diseases, it is drug discovery for a few. Similarly, instead of having to pay for clinical trials for each and every disease over and over for different medicines, there is one clinical trial perhaps across many different diseases. These all have a major impact in terms of the overall efficiencies that we can build into the system with platforms like these. Hopefully, that will create a future world where access to innovation will be a bit more equitable, but there is definitely a lot of work to do across the entire system to address this.

Erika Berg (*host*):
We have talked a lot about the patient and the family role in the overall development of treatments for rare disease and how impactful that can be. Based on your experience, is there any sort of call to action that you would suggest? What effective actions could people in the rare disease community take to help drive curative therapies forward, or what have you observed in your experience?

David Fajgenbaum:
I shared earlier about the AI platform that we have built that is quantifying every drug with every disease. We also have a very simple, "bypass pathway", as I call it, and that is where patients

can go to everycure.org/insights, and they can share about a drug that they have received from their doctor and whether it has helped or not. We love when these insights come from our AI platform, but we also love when they come from patients who can share that this drug worked for them. Over 20% of prescriptions written every day in the US are off-label, so doctors are prescribing drugs for diseases that they are not approved for, all day, every day, across the United States. Like I said, it is between 20% and 30% of all prescriptions. So, when patients do receive something off-label, or when a doctor does prescribe something off-label and there is something interesting that happens, like perhaps some improvement in their symptoms or some early insight, we want to hear from you. We want you to come to everycure.org/insights and let us know. We are going to look at our AI platform score and see what it is from zero to one, but we are also going to note that it helped a real patient, and that is going to help to flag it so we make sure that we are moving it up in our list.

"When somebody gets a diagnosis like this and you feel like you are the only one in the world with this disease or you have never heard of it before, it can feel very isolating and extremely intimidating, but the reality is that you are not alone. Rare diseases are actually very common. One in every 10 people has a rare disease and one person can make a big difference. So, find your people and your network. If the network does not exist, build your network just like David did, and the collaborations that can be brought together to really tackle these difficult problems can move mountains."

Michelle Werner:

I think that there is one big call to action. When somebody gets a diagnosis like this and you feel like you are the only one in the world with this disease or you have never heard of it before, it can feel very isolating and extremely intimidating, but the reality is that you are not alone. Rare diseases are actually very common. One in every 10 people has a rare disease and one person can make a big difference. So, find your people and your network. If the network does not exist, build your network just like David did, and the collaborations that can be brought together to really tackle these difficult problems can move mountains. You do not have to settle or just wait for something to happen. There are things that you can do. You are powerful and you can make a lot of things happen. I think that is certainly something that I have seen from many of the families that I have interacted with, and I think that is something we can all learn from.

Bill Hobbs:

I agree with what has been eloquently said. I think the message is to keep doing what you are doing and do not give up hope, because it matters. It may not be today and it may not be tomorrow, but we still have hope. We had a public advisory committee meeting with the FDA for Casgevy, which included time for public comments. There was a patient advocate there who made a comment that sickle cell disease had been in her family for generations. Her hope was that she may not be the last that would have a child with sickle cell disease, but hopefully she would be the last to suffer so much. I think the compelling thing is to keep demanding, advocating and pushing forward, as the hope for future treatment options is something we aim to address over time and we really need those voices to help.

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