

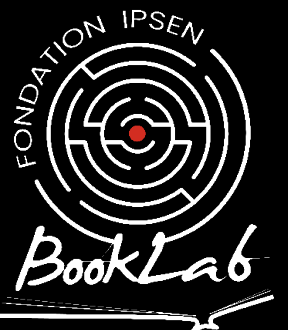
# The Rare Disease Gazette

*Conversations with  
the world's experts  
about rare disease*

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## PERSONALIZED THERAPIES



# Editorial

by **James A. Levine**

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Rare Disease Detection: Rare But Not Alone



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

The journal *Science*, (American Association for the Advancement of Science) in collaboration with Fondation Ipsen delivers international science webinars for the general public. In 2022, these webinars focused on building solutions to improve the detection of rare diseases. *The Rare Disease Gazette* is a magazine that broadcasts these discussions.

*James Levine*



## DON'T MISS!

### The Conversation

**Experts of the month:** Sean Sanders, PhD, hosts a conversation with world's experts about Personalized therapies in rare disease

# The Conversation

## Experts of the month

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

**Sean Sanders, Ph.D.** (Science/AAAS, Washington, DC)

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

**Genine Winslow, M.Sc.** (Chameleon Biosciences, San Anselmo, CA)

### Sean Sanders (host):

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

### Tiina Urv:

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

### Genine Winslow:

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

### Viviana Giannuzzi:

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

### Sean Sanders (host):

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

### Viviana Giannuzzi:

Precision medicine does not have a unique definition. In theory, personalized medicine is a therapeutic strategy tailored to an individual patient: the right person at the right time, based on its gene, lifestyle, and environment. Precision and personalized medicines are particularly relevant to rare diseases. We sometimes have one patient in a country or in a region, so precision medicine, personalized medicine, is a unique opportunity for a patient to be treated with the right treatment, or even to be diagnosed. We need a lot of efforts to develop these kinds of medicines, because it still represents, even today, a challenge for research, for companies, for institutions and medicines agency evaluators.

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

### Genine Winslow:

I work more on precision rather than individualized medicines. I work on gene therapy, and specifically gene replacement therapy. That means that we can treat a genetic disease that is generally caused by a defect in the patient's own gene by supplying that patient with a correct ver-

sion of the gene. This field is relatively new, although we, investigators and clinicians, have been making great strides. We focus exclusively on rare diseases for several reasons. It is a way to help people that have no hope, that have absolutely nothing else. It is also a way for us to get input from regulators, the FDA and European regulators, about our technologies in an accelerated manner. I think it is a very important space to be working in. It is where we can make the most progress with novel and cutting edge technologies. This is why, for most of my career, I have been working exclusively in the rare disease space.

From a drug development perspective - because that is what we do, we are developing genetic medicines - the challenge is to get specific showing clinical efficacy. This is a challenge in the rare disease space in general. Some of these diseases can take years to manifest. They can also take a year or two or more to show improvement in the condition. Our drug development models don't have a law assessing whether a drug is working in clinical trials. Our current system doesn't allow for slow, steady, continued progress in improving a patient's health. Particularly in rare diseases, regulators can work with us to develop new models, new ways to analyze clinical data, so that we can start to bring treatments for patients, even when the total number of patients with a particular type of disease is very small.

### Sean Sanders (host):

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

### Tiina Urv:

When I think of precision medicine, I think of the following: if you are treating a disease, you are looking at a target and you want to get right at the target. When you are looking at a disease that has a large number of patients, you have a large cohort of people that you can do the clinical trial with, and you try to find the best drug for the most people. Unfortunately, with rare diseases, you don't have that big number of people, and you also get the people for whom that drug doesn't work. You aren't finding that exact hit for that individual. That is what I think precision medicine is: you are looking at something that hits a specific target. Personalized

medicine is more linked to an individual, for example, at the N-of-1 trials where you only have one patient.

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

**Sean Sanders (host):**

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

**Tiina Urv:**

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

**Sean Sanders (host):**

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

**Tiina Urv:**

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

**Genine Winslow:**

Our clinical trial sizes are not necessarily an N-of-1, they are more an N-of-15, which is still a very small number. Typically, for a standard drug, you would have hundreds of patients enrolled in your first clinical trial. The way that we assess whether a drug is working is based on statistical rel-

evance with those large numbers of people, which is much easier to show when you have access to hundreds of people. The challenge is: how do you show meaningful significance when you don't have the luxury of hundreds of people? This is a road that is being paved as we speak for gene therapies. It is an evolving conversation. The overriding goal of regulators is to ensure that drugs work and are safe. The challenge is: how do we do that with N-of-1 or N-of-15? You hit on something that is very important when you are working with these very small patient populations: the patients are their own comparators. N means the number of patients in a clinical trial of 10 or 15. Sometimes, we do running studies, where we monitor the patients and measure, looking at the test we use, to determine whether or not the drug is working. We call it clinical N points. We show what these N points are in each individual patient before they have been given the drug and compare it to what is happening after.

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

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

**Viviana Giannuzzi:**

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

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

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

**Tiina Urv:**

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

**Sean Sanders (host):**

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

**Tiina Urv:**

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

**Sean Sanders (host):**

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

**Genine Winslow:**

Genome sequencing is now very widespread. When I say genome sequencing, I am not referring to sequencing the entire genome of something. I am talking about sequencing the part of interest, the part that you are working with. I have been in this field for a long time. 35 years ago, I used to do DNA sequencing by hand. We now have machines that do everything: all the chemistries, the reactions... everything is completely different now. Genome sequencing is like a work horse that supports the development of rare disease drugs, anywhere from cancer to rare genetic diseases like those that I work on.

We have used genome sequencing to figure out why one patient, for example, will respond to a cancer drug, and why another patient with the same type of tumor won't. We have used genome sequencing to dive more deeply into different types of

diseases, and try to correlate on a DNA level, how to help particular patients respond better to a drug or a type of drug. Genome sequencing used to be much more expensive. Remember when they celebrated sequencing the entire human genome? It has come so far, even since then, that it is relatively inexpensive. We can sequence very large amounts of DNA in a fraction of the time that we used to be able to. It has changed quite a bit and for the better, and it has become a very common tool that we can use to better understand a patient's particular disease, and the reason why they might be responding better than another or worse than another patient in the same clinical trial.

**Sean Sanders (host):**

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

**Viviana Giannuzzi:**

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

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

**Sean Sanders (host):**

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

**Tiina Urv:**

I like the term "treatment odyssey" as well. The diagnostic odyssey is something that families go through. I am not a patient or a family with a rare disease, but I spend a lot of time talking to the families and to patients with rare diseases and hearing their stories. What you hear repeatedly is that they just want to know what is causing it. The first thing they want to know is "What is wrong with my child?" or "What is wrong with me?" They often say that once they find out, it is a big relief. However, it can take between three and eight years, with the average of five years, to get a diagnosis. In that time, they are usually seen by at least seven different doctors. The current model is to go to your primary care

physician. If they can't figure it out, they spend a little time trying to diagnose you. If that doesn't work out, they send you to the next person, and if that doesn't work out, they send you to the next specialist. We need a centralized place where, if you can't be diagnosed in X amount of time, you should be sent to a broader team of people that look at you from multiple directions – for example, neurological or digestive – to find out the different reasons why you could be having these problems.

***“We need a centralized place where, if you can't be diagnosed in X amount of time, you should be sent to a broader team of people that look at you from multiple directions – for example, neurological or digestive – to find out the different reasons why you could be having these problems.”***

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

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

**Sean Sanders (host):**

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

**Tiina Urv:**

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

**Viviana Giannuzzi:**

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

**Sean Sanders (host):**

*Genuine, could you please share your thoughts on the treatment odyssey as well? Could you also speak a little bit more about the gene-based treatments that you are looking at it at your company, and particularly the viability of these as a broader treatment for rare diseases? You said that things are quite specific at the moment, it is quite a new*

*area. But is there something that you believe will be viable to treat rare diseases more broadly across the world?*

**Genine Winslow:**

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

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

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

***“All children deserve access to the latest genetic testing, because if they are unfortunate enough to have been born with a severe genetic disease, they deserve to know what it is no matter where they live in the country.”***

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

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

**“We are starting to discover why [gene therapy] works very well in some patients and it works less well in some other patients. For gene replacement therapy, we are finding it has to do with the immune response to the drug. The immune response generated by each in-**

**dividual patient can influence how well that drug works for a particular patient. My company has been working on a way to neutralize that immune response so that we optimize the efficacy or how well a drug works for more patients.”**

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

**Sean Sanders (host):**

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

**Tiina Urv:**

About newborn screening, there is a uniform screening panel that is recommended by the Health and Human Services. To be added to that panel, which most states pick up, the disorder must have some

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

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

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

support that, such as people, jobs, knowledge and sharing and pooling of information. That is a dream world.

**Genine Winslow:**

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

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

*"If we had the entire genome sequence, we wouldn't know what to do with most of it. Therefore, for now, we focus on those that we know, or those parts of the genome that we know, or suspect could be causing a disease."*

**Viviana Giannuzzi:**

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

On the other hand, again, we need to ensure that patients have safe and quality drugs. This is the role (sometimes the unfortunate role) of the regulators. The problem is that these are the most challenging drugs. We need more expertise. Another important challenge is that we don't work

with pills: we work with cells and genes. The challenge is to have equipment and facilities at each level, regional and local, to provide patients with this drug across-the-board.

**Sean Sanders (host):**

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

**Tiina Urv:**

Orphan drugs don't necessarily need to be in rare diseases. They can be treating neglected diseases. A lot of people could have it, but basically, it is not in the best financial interest of a company to invest money into working in an area where there are only a few people who need it, or, unfortunately, a part of the world that can't afford it. The FDA and the government wanted to push people and give them the incentives to work on those treatments. It has been 40 years, it could have done a lot more, but it also could have done a lot less, it is hard to say. Between 1983 and 2019, 5,099 drugs and biologics received orphan designation. The top three areas that are receiving orphan designations are firstly, oncology cancer. If you are a lump or splitter, it is like each cancer could be rare because if you start looking at individualized medicines, everyone's tumor is a little bit different in how you treat it and how you adjust the drugs for it. For rare diseases, we have learned a lot from cancer. The second top area receiving orphan designations is neurology. The third one is infectious disease. Also, the one area that has recently started to come up as well is the pediatric diseases. So, we haven't cured all the problems, but it is better than having nothing and no incentives as of this time. In the future, things could be different or modified. We could have worked faster, but there is no guarantee with any ideas that we have did something.

**Sean Sanders (host):**

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

**Viviana Giannuzzi:**

Orphan medicines need specific support from institutions and governments, otherwise they are likely not to be consid-

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

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

**Sean Sanders (host):**

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

**Tiina Urv:**

It is slow progress.

**Sean Sanders (host):**

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







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