The Rare Disease Gazette

Conversations with the world’s experts in rare disease

Issue #1 | April 2021

RARE DISEASE DETECTION

episode 1
The plight of patients with rare diseases is a critical unmet need of patients in healthcare. 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 2021 these webinars focused on improving the detection of rare diseases. The Rare Disease Gazette is a magazine that broadcasts these discussions.

If you would like your Association featured in future issues of The Rare Disease Gazette please drop me a line at: james.levine@ipsen.com.
The Conversation

Experts of the month
Flaminia Macchia, MA
Peter A. Merkel, MD, MPH
Sean Sanders, PhD
Tiina Urv, PhD
Durhane Wong-Rieger, PhD

Sean Sanders, PhD:
Hello, everyone and a warm welcome to this brand new Science and Life Webinar Series on “Rare Diseases: Their Basis and Burden.” I’m Sean Sanders, Director and Senior Editor for Custom Publishing at Science. In this new nine-part series that will run through the remainder of 2021, we will focus on a topic that is often ignored, but is critically important, that of rare diseases. The term is something of a misnomer since collectively the approximately 7000 disorders that come under the rare diseases banner, in total affect about 300 million people globally, including one in 11 Americans and over 30 million people in Europe.

Our discussion today will be intentionally broad as we introduce you to the most critical challenges for patients, doctors, and families facing rare diseases. These include limited testing, lack of diagnosis or inaccurate diagnosis, lack of research coordination, and limited availability of treatment, to name just a few. In subsequent webinars, we will delve more deeply into these individual topics, so please look out for those events. If you’d like to sign up to be alerted about future webinars, you can follow the link in the resources tab just to the right of the video. I am delighted to bring you a wonderful group of experts who will help us understand this topic.

Now I’d like to give our guests a chance to introduce themselves. Perhaps we can start with Dr. Tiina Erv from NIH. Over to you, Tiina.

Tiina Urv, PhD:
Hi. Thank you for having me. I’m delighted to be here. I work at NIH, in the Office of Rare Disease Research. The Office of Rare Disease Research is located in NATS, which is National Center for Advancing Translational Sciences. The program that I work most closely with, and happily with, is the Rare Disease Clinical Research Network, which is a network of consortia. We have 20 different consortia that study at least three different rare diseases, and they work very closely with the patient advocacy groups, the research community, and NIH staff. Thanks.

Dr Sean Sanders (host):
Wonderful. Thank you so much, Tiina. Next, we’ll go to Durhane Wong-Rieger, Durhane.

Durhane Wong-Rieger, PhD:
Thank you very much, and I’m so pleased to be here, Durhane Wong-Rieger. I am first and foremost, a parent of two children growing with rare conditions. My daughter, in fact, has never gotten a diagnosis, so it’s always been a matter of trying to kinda decide what to do and certainly having no road map in terms of what prognosis might be, though she’s doing great. My son was actually diagnosed on birth, and actually had a pretty established plan in terms of what his follow up in treatment should be. I’m also a psychologist by training and profession, though for the last, oh gosh, the last 20 or so years I’ve been working full time as a patient advocate.

I am president and CEO of Canadian Organization for Rare Disorders, which is a national umbrella group for rare diseases. I also serve as chair of the Council for Rare Diseases International. I lead on the Patient Advocacy Constituent for the International Research Consortium for Rare Diseases, where in fact the patient community works alongside of funders, alongside of researchers, in directions for diagnosis and new treatments. I also have a number of other international groups, I work with the Asia-Pacific Alliance of Rare Diseases Organization, where I’m president, and also I am the patient advisor into the APEC, the Asia-Pacific Economic Cooperation, on the rare disease framework. So, have a lot of roles internationally, but really work a lot also with patients on the ground here, especially in Canada.

Dr Sean Sanders (host):
Alright. Thank you, Durhane. Our third guest is Dr. Peter Merkel. Peter, welcome.

Peter A. Merkel, MD, MPH:
Hi, thanks for having me. I am Professor of Medicine and Epidemiology at the University of Pennsylvania here in Philadelphia, in the United States. For the last 25 years, I’ve studied two families of rare diseases, scleroderma, and even more so, vasculitis, which a whole series of different disorders. I have privilege taking care of patients with these rare diseases and I’ve studied the science of actually how to study rare diseases. I am the international director of the Vasculitis Clinical Research Consortium, which is actually a member of the Rare Diseases Clinical Research Network that Dr. Urv spoke about, an NIH-sponsored international research enterprise. And we do clinical trials and other types of translational research and training. I also co-direct with an online patient research portal, and I work very closely with patient advocates, such as we have on our panel today, to advance rare disease research. I’m sure I’ll talk about that important partnership. So, I’ve been studying rare diseases for a long time, and I’m happy to be here. Thank you.

Dr Sean Sanders (host):
Alright. Thank you, Peter. And finally we have Flaminia Macchia. Flaminia, welcome.

Flaminia Macchia, MA:
Thank you for inviting me today. So I’m Flaminia Macchia. I’m the Executive Director of Rare Diseases International. I’ve been active in the rare disease space for the past 20 years. I was for 15 years at EURORDIS, which is the European Organization for Rare Diseases, and then for five years in the pharma company, and now I’m back to the patient advocacy side. Thank you.

Dr Sean Sanders (host):
Great. Thank you, Flaminia. So, let’s get started with our discussion. I’m going to start with a very basic question. When I started looking into rare diseases, it’s not an area that I knew about. My background is microbiology and cancer research.
What I found interesting is there are many different definitions of rare disease, depending essentially on which country you’re in. So Peter, maybe we can start with you. Could you help us understand what defines the rare disease?

Dr Peter Merkel:
Yes, so a rare disease actually is interestingly defined by different countries or regions. Rare disease in the United States is defined as a disease with a prevalence of 200,000 people or less, or it’s a disease that is relatively rare and understood, of which we need more therapy. Rare diseases are also referred to as “orphan diseases” in some countries, and the term is often used interchangeably, but it’s not necessarily exactly the same, and I think different countries do it. I would say this about a rare disease. A disease is rare until you or someone you love gets it, and then all of a sudden you know a lot about it and you’re looking around. But it can be difficult, and so that’s why rare diseases have been singled out for study, both because we need to advocate for those patients, and scientifically, it is extremely helpful.

Dr Sean Sanders (host):
Durhane, let me come to you. I remember watching your YouTube talk that you gave about rare diseases and you’re work in Canada, and I saw you shaking your head a little bit when Peter mentioned “orphan...”, the term “orphan diseases”. I know you have some thoughts on that.

Dr Durhane Wong-Rieger:
Yes, and it’s not a disagreement necessarily, but there are no such things as orphan diseases, and rare diseases that Peter I think has indicated means a whole host of different things. And when we work globally, we know every country will have its own definition. In fact, you go to Taiwan, you go to China, rare diseases, whatever the country designates as a rare disease. It does have the commonalities as Peter says, is that they are... They affect usually small numbers of people, they are notoriously difficult to diagnose, they may be severe, they may be progressive, which is built into the European definition, but they are also under treated and oftentimes neglected. The commonalities, again are greater than the differences when we go across countries. And I think from a patient community, we’ve kind of convinced people it isn’t worth worrying about what’s the definition of a rare disease.

A rare disease is as Peter says, is something that will affect a few number of people. It’s a commercial term if you know, it originally came from the US who basically said, “These are a number of diseases for which we cannot get drugs developed because it’s not commercially viable.”, and they were called “orphan drugs”. Diseases aren’t orphan, it’s the drugs that are because companies would get them to a certain point of development then they leave them on the shelf, they orphan them. So I think that’s the challenge. And so in different countries, it does mean different things. Even within one country, you will not find from a policy level to a clinical level to an access level that the same definition is used. Knowing always it’s difficult to diagnose, difficulty to treat, and definitely deserving a whole lot more in terms of every spectrum, from diagnosis, to access, to care, and support.

Dr Sean Sanders (host):
Flaminia, could I ask you to jump in with your perspective from the European side of the world?

Flaminia Macchia:
Well, it’s not a European side, it’s more international one for sure. The impact of a rare disease is very much linked to the rarity, which means that there is generally speaking, a lack of understanding, a lack of knowledge, a lack of expertise, and it’s really the impact on people’s life that are of most interest to us. Thank you.

Dr Sean Sanders (host):
Alright. So Tiina, I’m going to come to you with the next question about how rare diseases arise. I think... It seems to me that a lot of what I’ve found in the research is about genetic rare diseases, but there’s also non-genetic rare diseases. So I wonder if you could talk about the types of rare diseases we have. I mentioned at the start, there are about 7000 of them.

Dr Tiina Urv:
So there are a lot of different types of rare diseases, and there are also many different causes of rare diseases. The majority are thought to be genetic and these are directly caused by changes in the genes of the chromosomes. In some cases, genetic changes that cause the diseases, they come from one generation to the next, but some are spontaneous so you don’t know if and when. All of a sudden you have a child with rare disease or you yourself develop a rare disease. It can come out of the blue and I think that sometimes those are the cases that are the hardest to identify and diagnose. In other cases, it can just be random. Many rare diseases include infections, some are cancers, some are related to autoimmune diseases that aren’t inherited, and every day we’re looking for more causes and different ways to understand where these disorders are coming from and what causes them.

Dr Peter Merkel:
I would add, rare diseases are disproportionately represented by genetic disorders because even one small mutation can cause these. But it is by far not the full story, and I think it’s important to... As I agree with Tiina, there is a lot of genetic rare diseases, but there are a lot of rare diseases that do not have a genetic basis or do not have a solidly genetic basis. And I think that often put... People sort of wondered, “Why? Why did I get it? Why did my family have it?”, and sometimes there are other reasons. And just like with common diseases, there is a mix of a genetic component and environmental component and infection component and various things that cause disease. And that is the definition of what a disease is. We keep slicing them up by saying this subgroup might have this genetics and combined with this environment. And so it gets pretty complicated. Genetics have been a tremendously powerful tool for us to understand and diagnose disease and actually help lead towards treatment. But it is one of the many components, and I think it’s important for people realizing that we study it across because the treatment benefits may come in a variety of ways.

Dr Tiina Urv:
And... Oh, I’m sorry. And Peter, that kind of jumps off on to when you’re counting how many rare diseases there are, is are you lumping or are you splitting the diseases? Because some disorders have a spectrum that you can have the same disease, it’s on a spectrum, and some people will count that as one disorder, and others will split each different gene defect into a new disorder. So that’s where it also becomes complicated. In the counting, the identification of the disease, and the training of the disease.
Dr Durhane Wong-Rieger:
If I can just jump in, I think those are amazing... Really important aspect as well. I think they’ll recognize that. As you say, it depends on how you want to define it. How do knowingly specific you’re going to get. That’s going to make a difference. And some of the more common diseases as everybody knows, we’re now getting these sub-groups that in some respects, they actually become like rare diseases for all the reasons that we talked about. So that also complicates it, especially in cancers as we’re starting to talk about more precision medicines. I think there is an inordinate bias towards genetically causative rare diseases because we can now with the genetics... The way they are... We can actually begin to diagnose them, we can define them. Whereas the others are still much more difficult to get to a diagnosis. And we do have patients who come to us, and our organizations is, “How come you’re forgetting us? We do not have a genetic disease and nobody’s talking about us anymore.” And I think that is a very, very important case. And I think, as Peter says, many of these genetic diseases are also very much influenced by the environment, so that makes it also very complicated in terms of rare diseases.

So I think we risk being very reductionist if we just start to look at what are genomic definitions... And we just focus all of our attention in terms of being able to do genomic sequencing and getting finer and finer definitions based on just genotyping, and we’ll miss some of the bigger things that I think we’re all concerned about. And that is what’s the impact in terms of patients, what else do we need to do? So I think all of those things are important. The other thing to say is that, two important things... That about 95% of persons with rare diseases will have already been identified within the most common rare diseases. So that’s important to know. Many of the other diseases... We have a ultra rare... The other thing is that we’re missing a lot of rare diseases because we’re not looking at it. Most of the work has been done in North America, Western Europe... Rare diseases in Africa, rare diseases in Asia, rare diseases in Latin America... We’re missing many of those because nobody’s looking at them. So we also have patients who are saying, “What about us?” So I think as researchers, as patient advocates, as whatever we’re trying to do here... We I think are being increasingly pressed to say, help about the equity in terms of identifying more rare diseases. We have very rare and neglected diseases, even among the rare diseases.

Dr Sean Sanders (host):
Mn-hm. Great. Flaminia, did you have anything you wanted to add?

Flaminia Macchia:
No, just to say that indeed, if we focus only on the genetic rare diseases, then we would leave aside a good 30% of the population, which because a good 30% of rare diseases are rare cancers, rare infections, rare poisoning from food, from medicines, drugs, chemicals... So just to underline. Yes, it’s rather...

Dr Durhane Wong-Rieger:
We can look at them as real successes right? And the goal is to keep them very rare.

Dr Peter Merkel:
We you sometimes forget that lesson. Polio is just about... Was close to being eradicated and still not, and we could do that. And so we have... Small pox has been eradicated. We can do this if we work on a worldwide basis.

Dr Tiina Urv:
And I will say, in relation to the autism question, is there a lot of rare diseases that fall under the umbrella of autism where you have disorders like Fragile X Syndrome, where autism, it co-occurs with a rare condition?

Flaminia Macchia:
Yes. A lot of autisms have underlying cause. A rare disease, Rett’s Syndrome... And you name it, many... Yes. It can be a symptom.

Dr Durhane Wong-Rieger:
Yes. We’re very excited by some of the work that’s actually... I think is going into autism to begin to actually identify many of the sub-groups within autism. We kind of lump them all together. Another common one that we kinda lump together is epilepsy. Epilepsy is not... Epilepsy is not epilepsy, is not epilepsy... There are many specifics there.

Dr Sean Sanders (host):
So this has been a great discussion because you’ve really touched on some of the major challenges that I did want to talk about. The one that we haven’t really spoken a lot about is testing and the role that doctors play, primary care doctors in identifying potential rare diseases. So Flaminia maybe I’ll come to you with this one. What are your thoughts on education of doctors and also improvements in testing for rare diseases? Where do we need to do the work?

Flaminia Macchia:
Well, this is actually one of the initiatives of Rare Diseases International, partnering with WHO, is to create, to develop the concept of a collaborative global network
Dr Peter Merkel:
I agree with that. I think this brings up a lot of important issues of education and access to proper care. We range from wealthy countries with big infrastructure, access to lots of specialists to countries where you can’t get basic care, unfortunately. And so I think it’s actually unlikely that we’re going to be able to educate all primary care physicians to understand rare diseases, but one of the biggest rules as a practicing physician is know what you don’t know. And when you identify something that I don’t know what this is, you get help, you go to a specialist, you go to one of your colleagues. I think that’s what we really want. And we need to make sure patients have the ability to get that help and to go to a specialist. And that can be a cardiologist, a rheumatologist, a surgeon, it depends. It can get more and more specialized depending on the problem and people tend to keep hunting till they find an answer. It’s very frustrating not to have one. Although sometimes that is the answer for now.

And it goes everywhere from the primary care to highly specialized centers such as ours, which are centers of excellence for various, many, many different rare diseases, to an even more specialized, I want to mention, which is that the NIH sponsored something called the Undiagnosed Disease Network. Actually here in the University of Pennsylvania, we’re now a site for that, and I’m part of that program. And that’s patients are sponsored. They get a letter from a physician and he looked to see, “Can you help me understand my disease?” Unfortunately, not all of the patients who apply can be seen by any means, but that program is trying to say, “Okay, even when you’ve seen specialists, maybe we’re missing something, so we screened for it and maybe we can bring some very specialized scientific tools, genetic, metabolomic, other things, to identify either your disease or a new one that we can identify, but that is very specialized, a few people in a very wealthy country such as ours. I think the spectrum is there, what we’d like to make sure is that people have the opportunity to have additional evaluations when it’s not, if something’s not working right, is something wrong?

Dr Durhane Wong-Rieger:
Can I add to what Peter’s just saying because I think what he says is so important in terms of getting to the right specialist and having those kinds of sites, and certainly the unidentified rare diseases centers in the US have been a real example of what could be done, but very limited in terms of the accessibility. One of the... Obviously the biggest challenge for patients and parents as well, is just getting some money to recognize the fact that there is something that is not ordinary. I mean, we go back to... And this is why we use the zebra so much in rare diseases, because it’s the old training, you look for what is common. And sometimes it can be very frustrating for parents, and especially here we think it’s so amazing for her child when the physician says, “I don’t think so, I don’t think so. Just go home”, and we have so many examples of that. We found, in our own surveys, it can take up to seven years to get a diagnosis with up to 14 misdiagnoses along the way, because you can’t get to the right person. So, a lot of things are being done, I think, to help bridge that.

We have a global commission to end the diagnostic odyssey for children with rare diseases, which is really first and foremost educating patients and parents to actually be aware, but it doesn’t do any good if the healthcare professionals, the front line are not also... It’s not just the education and awareness, and I think, Peter, you would know it’s that it’s very frustrating for these physicians if they got nowhere to go. You have a parent that keeps banging on your door and says, “I really think something’s wrong”, you’re kinda going like, “I got nowhere to go”.

Dr Durhane Wong-Rieger:
We need to get better tools to them as well. And the AI is doing a great deal, there’s a whole lot more that’s being developed in that area, not fast enough, not available enough, but that’s actually happening. Scleroderma is one of those especially that we think is so amazing in terms of the kind of work that’s being done to educate frontline physicians around Scleroderma, which is difficult. I don’t know why I’m telling you this, you know this a whole lot better than I do. But we work with the patients, they tell us these are multi-systemic issues that will show up in different ways, and so trying to get my physicians the tools so they can actually intervene I think is so important. So, it’s that empowering, and again the Scleroderma community is a big one, empowering the patient to be partners with the physicians to help improve that diagnosis I think is so essential. And then after that, you need to have all of the other things that Flaminia and Peter were talking about, but if we can’t get over that first hurdle and if parents keep falling into the pit of nobody wanting to believe them or to take it up, then we can’t get them into where all of these resources could be available.

Dr Sean Sanders (host):
Great. Tiina, could I have you talk a little bit about what is happening at NIH? And then maybe I can come to Flaminia about the funding that’s available in international agencies.

And I’m thinking particularly of basic research, how is basic research being funded at NIH and how is it being funded globally, and is enough being done? So, Tiina let’s start with you.

Dr Tiina Urv:
The NIH is doing a lot of basic research in the area of rare diseases. I think that if you look at the NIH as a whole, and you look at what they do is... One thing that people forget is there are 27 different institutes and centers at NIH, and all of these centers are looking at multiple different diseases. So, it’s not just one center or one office, like the office I work in is the office of rare disease research. We’re not the only place that rare disease research takes place at NIH, every institute at the NIH is doing basic research in the rare diseases to gain better understanding in rare diseases.

The different types may fall into, if it’s a blood disease, it would go to Heart, Lung and Blood, if it’s happening in childhood, the National NICHD Child Health Institute would be looking at aging, would look at aging. So, the rare diseases are scattered all across the NIH. So, one thing that’s important to remember is there’s a group of people that are very interested in rare disease to come together to discuss where are we going, what’s happening, how is this happening, is there good communication. So, it may be difficult to search the NIH and say, “What are we doing specifically in rare diseases?” and find it. If you search under specific areas, you’ll able to find it because there are 7,000 diseases and we are looking at very many of them. From the clinical aspect, there’s a lot of coordination with the clinical trials. We’re encouraging the basic scientist to work with the clinical scientist and have
good communication back and forth. So, there’s a great deal. Peter has benefited greatly from the NIH in his great work.

Dr Peter Merkel:
NIH generously funded a variety of different rare disease initiatives and trials. And I would say, you ask about funding and I’ll jump over to, I’ll let Flaminia say internationally. You know, in the US and abroad, I work with lots of people around the world, and I think there’s government-sponsored science like the NIH to investigators at individual centers. There’s a lot of rare disease research hiding complain site, because people are looking at a particular pathway, a particular thing, any rare disease as a model for that. It’s not always, I’m going to find these patients to study that, it’s sometimes something else that’s going on, and then linking that is what’s important. From an international, there’s a lot of funding in other countries that are done. There’s also an increasing amount of funding from the bio-medical and biopharmaceutical industry, and there’s a reason for that.

It’s an incredibly lucrative at an industry that’s made a lot of money, and they have found that it is in fact profitable to make drugs for rare diseases because they’re able to charge a good amount of money in a variety of countries to make it back, and there is a market, people want. We’re in desperate need for proper treatments in rare diseases. We can talk about the economics of this and the fairness of this, but the fact is it was driven research that’s being done in these rare diseases. And I think it’s important to remember researching rare diseases can have a benefit for many common diseases and vice versa, researching common diseases can have great benefit for research in rare diseases. There’s not a dividing line, a wall at our... Down the hall here, and so we do it. But I think internationally it varies, but there is increasing interest in being able to sponsor researching rare disease, and maybe Flaminia can speak to that as well.

Flaminia Macchia:
Yes, so very briefly, what I can say is that as RDI’s, or at international level, what we can try to do we are trying to do it, is to provide a platform for discussion with pharmaceutical companies to develop specific strategies for low and middle income countries. Because if pharmaceutical companies directly apply their access strategies everywhere in contexts that are extremely diverse, we will not get to a position where we leave no one behind. We will certainly leave, many, many persons living with rare disease behind. And I’d like to underline that it’s not only about the costs. It’s really about how do we develop specific strategies for the needs and the specificities in the local countries, local regions, local markets, if we want to call it this way. So this is really an appeal, and we try to promote this type of dialogue.

Dr Durhane Wong-Rieger:
Can I just add again on the international level though? And RDI is a member of the International Rare Disease Research Consortium, of which NIH, of course, is a huge partner. Chris Austin was just a former chair of that consortium. And the goal with the consortium is to bring together, internationally, all of the researchers in rare diseases. So there are certain countries that are investing in rare diseases, there is industry that is investing in rare diseases, and there are other kinds of research foundations, etcetera, that are investing in rare diseases coming together to do collaborative programs. And that actually has a huge value obviously, because it makes sure that people that are working in similar areas are actually able to coordinate, and collaborate, and work together. It also means that there’s that kind of sharing in terms of the actual resources that are there and a real focus in terms of what the goals are. And there are some very specific projects within there, some of that Flaminia and others have alluded to.

And it’s been hugely important that major countries and major institutes like the NIH have also taken a huge role in it. So it’s probably one-third, maybe, is coming out of North America, and a third coming out of Europe, and a third coming out of other countries, Japan, China, other countries that are doing the research in rare diseases as well, coming together. So I think the more we can encourage that collaboration, the more we will be able to see some of the benefits coming out of it. And I think... And recently, over the last five years, they’ve introduced, as we said, a specific patient consortium in there recognizing the importance of having patients involved in many of these collaborative projects. So this I think is hopefully a way that we can bring some of that pooling, or also not just the knowledge, but of resources together.

Dr Peter Merkel:
Sean, I just want to add, I think from a clinical research standpoint, when you’re trying to bring therapies in diagnostic testing, it is almost essential in many diseases to work internationally. Rare diseases are in fact rare, and therefore it’s hard to recruit to get enough patients to study it properly, because you still need to do proper science and proper studies. And I think what we have seen in fields achemen and others, those fields that have advanced the most have had the most international collaboration. I was involved in helping, honored in with others to direct some international studies, and we have had studies with up to 100 sites in four or five continents, and it is only with international can you often get enough patients to study properly to do this. So there is both... It’s both scientifically enriching, and it is practical to work collaboratively in... Especially in the clinical research space.

Dr Durhane Wong-Rieger:
Yes, well, I can be very brief, because it’s really a matter of the overall healthcare systems. It’s not only... Actually, it’s about the healthcare system, but also about the social system, so there is a lot of improvement that we need to happen in order for countries everywhere, low and middle income countries, to be able to integrate all what can be offered. So this is... I know that Durhane, you’re very active in that as well. I mean, the focus on low and middle income countries is something we really need to promote. I cannot tell you now how exactly we will do that, but we need to start to put the problem of rare diseases at a level which is truly global. We need to integrate all different stakeholders, we need to discuss together, and we need to define some strategies that are more specific to low and middle income countries that we have done till now. So I don’t know, Durhane, you want to add something maybe in this.

Flaminia Macchia:
Yes, so very briefly, what I can say is that as RDI’s, or at international level, what we can try to do we are trying to do it, is to provide a platform for discussion with pharmaceutical companies to develop specific strategies for low and middle income countries. Because if pharmaceutical companies directly apply their access strategies everywhere in contexts that are extremely diverse, we will not get to a position where we leave no one behind. We will certainly leave, many, many persons living with rare disease behind. And I’d like to underline that it’s not only about the costs. It’s really about how do we develop specific strategies for the needs and the specificities in the local countries, local regions, local markets, if we want to call it this way. So this is really an appeal, and we try to promote this type of dialogue.

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Sean, I just want to add, I think from a clinical research standpoint, when you’re trying to bring therapies in diagnostic testing, it is almost essential in many diseases to work internationally. Rare diseases are in fact rare, and therefore it’s hard to recruit to get enough patients to study it properly, because you still need to do proper science and proper studies. And I think what we have seen in fields achemen and others, those fields that have advanced the most have had the most international collaboration. I was involved in helping, honored in with others to direct some international studies, and we have had studies with up to 100 sites in four or five continents, and it is only with international can you often get enough patients to study properly to do this. So there is both... It’s both scientifically enriching, and it is practical to work collaboratively in... Especially in the clinical research space.

Dr Durhane Wong-Rieger:
Yes, well, I can be very brief, because it’s really a matter of the overall healthcare systems. It’s not only... Actually, it’s about the healthcare system, but also about the social system, so there is a lot of improvement that we need to happen in order for countries everywhere, low and middle income countries, to be able to integrate all what can be offered. So this is... I know that Durhane, you’re very active in that as well. I mean, the focus on low and middle income countries is something we really need to promote. I cannot tell you now how exactly we will do that, but we need to start to put the problem of rare diseases at a level which is truly global. We need to integrate all different stakeholders, we need to discuss together, and we need to define some strategies that are more specific to low and middle income countries that we have done till now. So I don’t know, Durhane, you want to add something maybe in this.
but their social and their economic development. So that's really important, having rare diseases in there, as we did two years ago with Universal Health Coverage. Again, as Flaminia says, it's not just a matter of... Are we doing anything for rare diseases? In many countries, what are we doing about healthcare, and how much of that is a priority? So Universal Health Coverage, really, again, pushes the countries to say, “You cannot have the economic development, you can not develop on the social development goals of the UN unless you're actually taking care of the health of people.” So urging countries to bring in Universal Health Coverage, and within that we asked for and we got a special line to recognize rare diseases in there as a neglected population. So, it's making sure that as countries are doing more in terms of their health and economical and social development that they don't forget the rare diseases, we can't wait until you've come, you've got everything in place. So, that's been really important.

I think beyond that, of course, there are a lot of bottom-up strategies. It's working with countries and empowering countries to actually do things on their own. I heard the most amazing story about the geneticist in the Philippines who had introduced newborn screening, talking about diagnostic programs, you know. That's so important, one drop of blood, you can identify up to 60 genetic diseases. And in the Philippines, they introduce the program on newborn screening for a number of metabolic diseases. It was in the middle of a typhoon, and she's saying, "Oh my gosh, I've got these samples and I have to get them to a lab in a certain amount of time". She got the Coast Guard, she got the police, she got the people there, and she says, "We have 400 islands", they went from island to island picking up the samples to get them to her laboratory in time to have them test it in the middle of a typhoon. This was the commitment to having these then. Support those local initiatives, making sure that local clinics, local specialists, local GPs, paediatricians are also brought into it.

So, I think it's working, you know, top down, it's working bottom up. And beyond that, it's also we're looking at strategies that, as we're investing in these, we're asking for investments that will be global. The same as can do for vaccines, the same as we do for infectious diseases, right, the same as we do for some of the cancers. Let us have those kinds of multilateral, multi-stakeholder consortia that can help us think about what do we do in terms of not leaving behind those low maintenances.

**Flaminia Macchia:**
If I may add, what is very important to underline here is that universal health coverage means three things that need to be combined together. So, it's more services covered, and in this case it's more services for persons living with a rare disease. It's a bigger population so it's more people covered, and it's less out of pocket by patients and families. So, it's three elements that need to be combined in order to get to universal health coverage. And as Durhane was saying, we are promoting rare diseases as a human right priority towards the United Nations, because it's the whole aspect of the life of people with rare diseases that is impacted.

**Dr Sean Sanders (host):**
Great. So, Peter, I want to come to you in a minute just to talk about the Orphan Drug Program, but before I do, Tiina, I wanted to bring you back into the conversation. So, according to the statistics that I've read, about 390 of the 7,000 diseases that are categorized as rare diseases affect about 98% of the rare disease population. So, I think Durhane might have mentioned this before, a fairly small number of diseases impact a large part of the rare disease population. How do we best allocate resources for optimal benefit? We talked a little bit earlier about leaving people behind, with 7,000 diseases to cover how can you possibly do that, and should we be looking at focusing our attention on those 390 diseases, and then what happens to those that have the really rare diseases?

**Dr Tiina Urv:**
I think that we need to think differently about how we're working on things. I think that the focus has always been on one disease at a time, and that's been very problematic. I think that what we really need to do is think of groups of diseases that can be studied together, clinical trial designs that can be done so multiple diseases could go through a trial at the same time. I think that groups just need to work more together. I think picking and choosing who gets to go first is not going to work. The science won't be there, because sometimes science might be there for one disease that one person has and we can have a treatment and a cure, and are you going to say no because it's one person? Of course not, but for that one person, you can learn. I think it's horrible to say, to make things cost-effective, we need to work together, and it's rare disease groups coming together and maybe using the same infrastructure to build a registry together, so they can be tracking the natural history of a disorder, so the cost isn't so much. The burden isn't on just one group, but on multiple groups together, to let a larger group let a smaller group dovetail and ride the coattails of the work that they're doing and collect their data. It's not an easy question, but I think that we have to work together, we need to come up with new models of working collaboratively rather than separating each disease and going disease by disease, because that's... It's not sustainable.

**Dr Peter Merkel:**
So, that was 40 years... I think it was 1983, Congress first passed the Orphan Drug Act. And so, it's important to remember that the Food and Drug Administration is directed by acts of Congress, and that's giving their charge for how to do things. The Orphan Drug Act, which has been amended since then, was really a fundamental change in thinking about studying rare diseases, they used the term Orphan Drug. And what it has allowed is it basically creates a easier pathway for drug approval and review by the Food and Drug Administration. The Food and Drug Administration does an extraordinarily comprehensive review of new drugs, there's a complex process, and to be honest, many countries look to the FDA for guidance because of the resources that we have put into the FDA. So, it has a very disproportionate impact on world health, and it's not alone, the EMA does a very similar approach, as do PMDA in Japan and other places, and they've done some similar work on orphan drugs since then.

But in the past nearly 40 years, what has
happened is it has said, we’re going to make it... We’re going to facilitate studying rare diseases and getting your drugs through the process and approved, we’re going to make it easier with not as large trials necessary. And it’s not really a short-cut. It’s scientifically very sound and safe, but it’s recognizing some of the unique aspects of rare disease and facilitating that. It also gives some protection to companies so they can keep their hands a little longer, etcetera. So it is both scientifically, logistically and business-wise helps stimulate work in rare disease. Has it worked? It has definitely worked. I think everybody would agree.

If you look at these graphs, the number of drugs approved for rare diseases has gone up tremendously since the Act was started. Even more so than the number of drugs that we’re getting anyway, which is quite a lot. And I think when you talk... And I work with companies to help to develop drugs and other things. They will say, having something actually labeled as a rare disease is helpful in their development program. And so it’s this actual stimulus. The government actually works. It is similar in Europe and in other parts of the world where this has been done. So this is a successful government intervention, recognizing a problem saying, “Let’s facilitate and make this work.” And it has been extremely successful in the United States and around the world. And so it’s worked well. And that’s what I’ll say.

Dr Sean Sanders (host):
Flaminia, are there similar programs that are internationally in other countries, or is this fairly unique to the US?

Flaminia Macchia:
No, there are other countries who have a similar legislation than you were from Drug Act. For sure, in Europe, there is the orphan medicinal products legislation. I know in Japan, there is something specific. Or maybe not, Durhane?

Dr Durhane Wong-Rieger:
No other country has really done the same as the US and Europe. Obviously, the EU came in as well and the EU was very deliberate. They said, “Oh my gosh, all the research is going to the US. We need an orphan drug act because we need to have research investment.” It was a deliberate... The effort, right? I mean, it makes sense. I will say what the US did really well at the same time. They not only did the FDA or the Drug Act. They brought in the NIH Office of Rare Diseases. That was huge, because it really added that research component to also help in the study of rare diseases, understanding causes of the rare diseases.

Those two together were powerful and the EU did much of the same. There are in fact huge research consortium that was funded by the EU. So again, those are the two power houses that really fuel the research into rare diseases and the development treatments of rare diseases. But this is where, Flaminia and I both talk about a lot, is that it kind of stops, because these are expensive therapies. Despite the fact that the US Act or brought in because these drugs were meant to be brought to... Given support to bring to market because they would never be profitable. They are in fact profitable and they’re very expensive in some cases because there are so few people.

But it means that in low and middle income countries, there’s no hope in terms of getting access. A startling statistic I saw was that in fact, fewer than 10% of the people for whom there is a rare disease drug actually get access to it... Even in the US and around the world, fewer than 1% of people who might be eligible for rare disease treatment get access to the treatment. This is a disaster. And part of it is diagnosis, part of it is having clinical expertise. And so for many talking about these collaborative global networks that they’re better diagnostic tools. But part of it is just because the economics of it are not sustainable for low or middle income countries. And I’m not faulting the pharmaceutical companies.

That is not my goal here, but I think unless we have better strategies or how we’re going to make these therapies available, we will have a continuing kind of divide between not just rich countries that can get this drug. It will be rich patients and rich countries that will get these drugs, and everybody else. That is going to not create a benefit. So we need to start thinking globally about how do we make these therapies available, and I think that’s a huge challenge. Some of the things are working well. The FDA has also step forth in terms of being able to do things like doing regulatory approvals that other countries are picking up. Not every country needs to do it’s own regulatory approval. Those are the kind of things, but we need the deliberate strategies for getting these therapies more globally accessible.

Dr Peter Merkel:
I just want to amend. I agree with all of that. I think that it’s important to recognize it’s not just a single act of Congress or a single act of the European Union. It also comes at the right time. There’s been a revolution in biopharmaceutical industry and the biologic drugs in these various things. Everything comes together. More general infrastructure for clinical investigation. Better drugs that are coming out at the right time, but you need all of these factors to come together, and it has. And then honestly, the success that some companies and diseases have had, breeds more success. People look to somebody and say, “Look, they were able to do that in rare disease. We could do that.” And now, most companies have a rare disease unit that they try to go forward on in terms of the... But government can make a difference. Look at what’s happened with the Covid 19 vaccine, SARS COV2 vaccine. It is pretty obvious that putting tremendous investment has stimulated that to be done. Now, on the flip side, we have the same distribution problem where we have it being given vaccination is going greatly in the much wealthier countries and is much slower and problematic in less wealthy countries. And we need to address that on an ethical international scale, but it does that we shouldn’t lose track of the successes, but we should try to spread those successes more broadly.

Dr Tiina Urv:
One of the things I think is really important, Peter, is that you bring all the players to the table who are involved. It’s very easy to sit on an interview like this and say, “We must do this and we must do that, and giving directions. And you gotta do it, we have to do it. It’s very easy, but bringing together all the players to the table, bringing together the patients, bringing together industry, bringing together the payers, the insurers, the medical associations, the doctors. Everyone needs to understand what responsibilities each group has and until everyone listens to all the players at the table, it’s not going to work because everyone’s going to be worried about their own interest. Clinicians have their own interest, industry has their own interest and responsibilities basically, but I think it’s important that we start bringing people together from various areas to talk about how can we actually make this happen rather than saying we must, but it’s the how that’s the problem right now.

Dr Peter Merkel:
You have an example in the not that distant past, which is, it’s not a perfect example, but care for patients with HIV infection was very much concentrated in certain countries, there was some international effort of coming together to try to improve
access in poor nations, and it was a combination of pharmaceutical industries, scientists, clinicians and governments and including with the US, and it really did make a difference. It’s not perfect, but it’s made a very big difference in the global epidemic of HIV, in being able to get drugs to other countries, so I agree with you, Tiina, and it was because people worked together and said, “We should do this.” So I think there’s a lot of good will, there’s ways to do this, but it’s complicated.

Dr Tiina Urv:
Yes, everyone wants to cure the patients, everyone wants treatment for the patients, but making that happen is challenging.

Flaminia Macchia:
But as you were saying, and we were... I think we all agree on one point for sure, is that we need to bring all these different stakeholders together, and this is the platform we are trying to create.

Dr Durhane Wong-Rieger:
There are lots of examples, there are lots of models, I think, as Peter says, HIV is one of them. There’s also the models on the consortium around infectious diseases and neglected and infectious diseases, there’s the whole vaccine Gabby approach to it, there’s the hepatitis C example of what was done when the WHO stepped in to say, “you got it, are you going to make it available, or are you going to have to outsource the drugs you know one way or the other right?” So I think it is very much the way, I see it as, how do we bring people together? How do we do it? But there’s lots of models, if there’s the will to do it, I don’t know, sometimes it seems overwhelming because then you think of how much this costs.

Dr Tiina Urv:
I think when it gets overwhelming is when you look at there, if you look at how many people have HIV and all cancers combined, and if you bring that number together, there’s still more people with rare diseases than have all those conditions combined. So it’s a big number, it’s a diverse group of people, how can we find commonalities so we can work together and say we’re doing this for rare diseases rather than we’re doing this for disease A, and then we’re going to do it for disease B, and it’s never going to happen, but I think we need to work as a community.

Dr Peter Merkel:
And the people’s voice matter, patient’s voices really matter. Elected officials listen sometimes to their electorate, and in fact, it is the advocacy by patient groups that helped push all of this along, it’s not... Scientists do it, visualists do it. It’s a lot of different voices moving things forward, patient advocacy groups have been very helpful, not just in partnering and research and helping us prioritize research, but in advocating for research and distribution in this space.

Dr Durhane Wong-Rieger:
But it’s as you say though, the both of you... It also has to be done in partnership. The patient voice out there, just being a shrill patient voice doesn’t do anything. We’ve got to... And I think we’ve seen some great examples in terms of how these partnerships, there’s an opening up in the research community, opening up in the clinical community, opening up in the pharma industry where the patients can actually have an effective voice, and I think that’s made for real difference. So I always say you can demonstrate on as much as you want outside the gates, unless you can get inside the gates, it makes no difference. So we have to be able to get to the table, we have to have a seat at the table, but we’ve got to do that as a partner as well. You’ve seen how people bang at the gates outside, otherwise nobody listens, but... But you have to have people brought in as well, so, appreciate that.

Dr Sean Sanders:
Great, well, again, you’re a fantastic panel because you’re just addressing all of the questions I was just about to ask, so what I really wanted to talk about, and I think close out with is this idea of cooperation and collaboration, which seems to be coming up again and again, it’s got to be global, there’s gotta be partnerships, so the two things that I wanted to just finish on is... We have just a few minutes left is, the first is, what are the... What’s the low hanging fruit, where can we make easy, quick changes that will bring more collaboration and cooperation? And the other piece that I wanted to touch on is what are the impacts at a personal level? And Flaminia I’m going to come to you for this and Durhane as well, you also... You have family members, children who are impacted by rare disease, so maybe we’ll just go around and each of you can talk to those, so what’s the lower hanging fruit that we can address right now? And what do you see is the more personal impact? So, Durhane why don’t we start with you?

Dr Durhane Wong-Rieger:
Yes, I don’t know about low hanging fruit. I kind of feel like we took all the low-hanging fruit already, I think we’re really being forced now to climb up into those trees and really work it hard the way Tiina and Peter and Flaminia were talking about. I think we need to make that those big efforts now, so I think we ate up the low-hanging fruit. So, for us in terms of patients, I think the impact is still there, and I have been so encouraged, I think by the ability of patients to actually have a voice and part of it is very much all the other consortiums, all the other sick homes opening up to recognize the value of the patient voice, this was not there 40 years ago when we first had the Orphan drug act. So I think it’s made a huge difference and I think we’ve increasingly become partners and use enterprise, so that for me is the way forward, so really, I think very much so in terms of appreciation of how much the communities have been able to come together.

Dr Sean Sanders (host):
Flaminia, why don’t we come to you next?

Flaminia Macchia:
Yes, so for me, it’s crucial to understand that all aspects of human lives are impacted by living with the rare disease far beyond on the health concerns. Of course, health concerns are extremely important, but the impact really go from the very beginning, from inclusion in kindergarten, in school, in university, that means inclusion in education, and this has a direct impact on employment opportunities. If we don’t change the working conditions, we don’t adapt the environment, we don’t adapt working hours, so this also impacts on the overall impoverishment of people leaving with rare diseases, the lack of autonomy. So it also impacts on the opportunities for leisure, for traveling, for social interactions, opportunities to develop a life’s project, even as pragmatic as getting a loan. And of course, there are huge aspects that are impacted by stigma and discrimination. So for families worrying constantly, social isolation, most parents become
primary caregivers. And so this they also have to stop working or having less working hours. And in this very often, it’s even worse for women, that often become the primary or even only caregiver. So we talk a lot about the impact, and I think there is an increasing understanding of the impact on people’s life when it comes to their patient aspect being their health concerns, but the overall impact is very often underestimated. And in terms of society, we talk a lot about the burden on society, but of treating, but did we really think enough about the burden on society of not treating? So I would finish like that.

**Dr Peter Merkel:**
I agree with all of my colleagues. It’s been a terrific conversation. I’ve really enjoyed it, stimulating. I think it’s important to keep working on respecting the scientific and societal impact of studying rare diseases as well as encourage the collaboration internationally. But really it’s about keeping rare disease in the conversation, in the conversation about healthcare, about society, about science and just keeping it in the conversation overall, as all of these issues are designed. There are some unique aspects that really are just very nicely put forward. And then there are some common aspects as well in the study of rare diseases. So as a physician scientist face rare diseases, keeping it... I learn from all of these aspects, but keep these diseases in the conversation as we create scientific programs, as we create legislation, as we create new avenues for healthcare.

**Dr Tiina Urv:**
I think a low-hanging fruit in my mind is getting people to come to the table and talk to each other. What is simpler than... Well, maybe not during COVID, but we can always Zoom, but bringing people and starting the dialogue between all the players. And that is not difficult because I believe that everyone agrees at the end of the day, we all want the same thing. We want treatments, we want cures. We want the patients to have better quality of life and to get the players to start talking to each other, to start making inroads of making that happen to get the treatments to the patients easier, to get the patients diagnosed faster. Until we all come together, it’s going to be very challenging. And so I think that is my final word.

**Dr Sean Sanders (host):**
Right, well, thank you so much, Tiina, and also to all of the other participants. We are out of time, so we are going to have to end our discussion here. Thank you once again to our fantastic panel and to Fondation Ipsen for enabling this conversation through their kind sponsorship. Goodbye everyone and thanks again.

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**Journal Club**

**Article of the month**


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**Take home:**
1. There have been two major eras in the history of gene discovery. The first was linkage analysis, where 1,300 disease-related genes were identified by positional cloning before the Year 2000. The second era has been powered by two major breakthroughs: the human genome project and development of massively parallel sequencing.
2. Massively parallel sequencing has hugely accelerated disease gene identification. In the past it took years to map genes associated with disease. Massively parallel sequencing lets genes be determined in weeks.
3. Massively parallel sequencing has ethical, legal and social implications. These concerns exist in common to all genetic testing but are especially relevant to massively parallel sequencing because of the amount of data generated. Examples include, relationship misattribution, finding genetic variants of uncertain significance, and issues surrounding genetic discrimination.
4. Massively parallel sequencing is rapidly transforming clinical practice and helping patients.