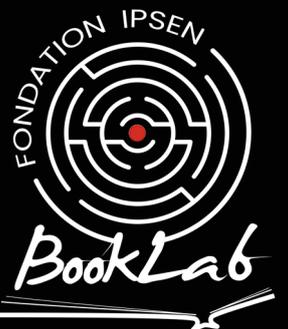


# The Rare Disease Gazette

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

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## HEALTH CARE



# 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 2021 these webinars focused on improving the detection of rare diseases. *The Rare Disease Gazette* is a magazine that broadcasts these discussions.

James Levine



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# The Conversation

## Experts of the month

**Dong Dong Ph.D.** (The Chinese University of Hong Kong, Hong Kong SAR, China)

**Eyby Leon Janampa, M.D.** (Children's National Hospital, Washington, DC)

**Helen Malherbe, Ph.D.** (Rare Diseases South Africa, Johannesburg, South Africa)

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

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

**Kym Winter** (Rareminds, St. Albans, UK)

### Sean Sanders (host):

*Hello, and welcome to this sixth installment of our Science and Life webinar series on rare diseases. I am Sean Sanders, and it is once again my pleasure to moderate our discussion today. In our nine-part series running through the remainder of 2021, we are looking at some of the most critical issues in the arena of rare diseases. You can find previous webinars in this series at [webinar.sciencemag.org](http://webinar.sciencemag.org), and the recording of this and future webinars will also be posted there. We have already covered quite a broad range of topics related to rare diseases, including the challenges of diagnosing and detecting rare diseases, neonatal testing, and the application of artificial intelligence in rare disease detection, diagnosis, and research.*

*We are going to examine the role that primary care doctors and frontline medical facilities play in detecting and treating rare diseases. Finally, thank you to Fondation Ipsen. We have a wonderful international panel of speakers today, and I am excited to have them introduce themselves to you now.*

### Durhane Wong-Rieger:

I am Durhane Wong-Rieger. I am President and CEO of the Canadian Organization for Rare Disorders, which is a national alliance of rare disease groups and patients. I also sit as Chair of Rare Diseases International, which is our global alliance of rare disease groups and international disease groups, and I am also

now President of the Asia-Pacific Alliance of Rare Diseases Organizations, which includes about 19 organizations across the Asia-Pacific area, which... It has been a very interesting experience because there is such a diversity, of course, in that region.

### Helen Malherbe:

I am Helen Malherbe. I am currently Director of Rare Diseases South Africa, which is a registered non-profit organization and public benefit organization here in South Africa, and we are really focusing on improving the quality of life for all of those affected by rare diseases and congenital disorders. I am a Director, but I am also heading up epidemiology and research at Rare Diseases South Africa. I have a foot in the academic world as well, being a Post-Doctoral Researcher. I am currently in between academic institutions, but starting again in September at a new organization that will be focusing on the health economics of rare diseases and congenital disorders in South Africa. Thank you.

### Eyby Leon Janampa:

I am an Assistant Professor at Children's National Hospital in Washington DC. I am also a clinical geneticist, and I have seen patients with rare disorders for over 10 years.

### Dong Dong:

I am Dong Dong, Research Assistant Professor from the Jockey Club School of Public Health and Primary Care at the Chinese University of Hong Kong. I started to study the social economic impacts of rare diseases on patients and their families, mainly in China in 2014. I used both quantitative survey methods and qualitative ethnographic methods to do my research. The research approach that I have been taking is basically called community-based participatory approach, which allow me to focus on the patient's real-life experiences and the impact of disease on their everyday life. That is why I also work very closely with the national patients' organizations in China, including the China Alliance for Rare Diseases, the Illness Challenge Foundation, and the Beijing Aili Myasthenia Gravis Care Center. Thank you.

### Sean Sanders (host):

*I wanted to start out by asking the broad questions about the problem, the problem of rare diseases and of detecting and diagnosing rare diseases. I found a quote that I am sure you have all*

*heard that is attributed to Dr. Theodore Woodward of the University of Maryland, where he said, "when you hear hoofbeats, do not expect to see a zebra." I believe the point he was making is, when you are diagnosing a patient, look for the obvious, but obviously when we are talking about rare diseases, that is not the case. In fact, it is the opposite. So, Durhane, maybe I can come to you and just ask, when it comes to diagnosing rare diseases, currently, how long does it take to receive a diagnosis?*

### Durhane Wong-Rieger:

Obviously, the time to diagnosis really depends on where you are, and it depends on the type of disease that you have got, so we are doing a much better job in terms of diagnosing what we might call common rare diseases. These are the rare diseases which do have a very clear, not only just a definition, but they can be much more easily diagnosed, they can either be diagnosed by a test, diagnosed by symptoms. It takes five to seven years for some individuals, when we ask people how long it took to get a diagnosis, and that is what the international experience is. The sad part about it is that most of these families also say, we get one to 14 misdiagnoses before we get to the right diagnosis, so that is a huge issue.

Obviously, with some of the breakthroughs in terms of newborn screening, in terms of genome sequencing, we can expect that we will be able to do a much better job in terms of diagnosis. But for the most part, and certainly around the world, we would have to say the challenge in getting a diagnosis is still very, very difficult, and certainly because there are so many rare diseases. It is not as if you can become an expert in rare diseases. There are still, as we say, 67,000 of them. It is still very, very difficult. 80% are genetic, so we are going to get closer to being able to do those kinds of diagnosis, but the access to that kind of diagnostic testing is obviously not widely available. For families, of course, for most of them, they are still going through that long period of time of not knowing and not getting an answer, and really, as we say, the despair of having a misdiagnosis.

### Dong Dong:

I want to agree with Durhane on her observation in the Canadian population. In China, we did several different national level surveys among rare disease patients in the past. In 2018, when we surveyed all the patients impacted by rare diseases

es, we did not select specific diseases, so we had almost like more than 100 different types of diseases, and we asked how long it takes for them to get a definitive diagnosis. On average, 58% of the patients can get a diagnosis in the same year when they start to see the doctors, which is very impressive. We did not expect to see these results, and if you do not take this part of patients into account the average time of this diagnostic odyssey is about 5.3 years. However, one year later, we have the first national list of rare diseases in China, so now we have 121 rare diseases defined by the government as rare in China. We surveyed 34 diseases from this whole 121 diseases.

Then surprisingly, nearly 80% of them can get a definitive diagnosis within the same year. And without taking this group of people into account, the average time for you to get a diagnose is 4.26 years, so it is shorter. The common rare diseases are not that difficult to be diagnosed. The most difficult part are the uncommon ones. Even among people with rare diseases, there are the common and uncommon diseases, rare or extremely rare disease are the ones that make a huge difference. Common rare diseases get a lot of public attention, like ALS. Because of the ice bucket challenge, lots of people know about the disease. So even before the ice bucket challenge, maybe lots of people have never heard about it, or even the doctors never seen any patients with that, but just due to one global social movement or this viral event on the internet, everybody gets to know it. These are the publicly well-known rare diseases.

The diagnostic odyssey is not that difficult, but what concerns us the most is for those who are not being detected, not being diagnosed, who can never find a diagnose in their entire life. We cannot survey them; they are not defined as rare disease patients in any way, they are not included in any of the databases, they are not included in any surveys. So, where are they? Who they are? These are the questions that we do not have answers for, and are there any other different ways for us to find them? Like, to discover the zebra among a group of horses. But, if we do not even have a definition for a zebra, then how can we find it? That is the thing, the question that concerns me or the other patients' organizations most.

### **Helen Malherbe:**

I am both jealous, envious, and encouraged just to hear the shortened diagnostic odyssey just described. The situation in South Africa is the same, but on a scale of magnitude, we are far behind in terms of even being able to diagnose obvious

congenital disorders. For example, Down syndrome, which is diagnosable within a couple of days elsewhere. There was a recent research study in KwaZulu-Natal, one of our provinces, where it can take over a year to get a diagnosis. Part of that is due to infrastructure challenges, lack of appropriately trained healthcare professionals, but also with other challenges in diagnosis with the clinical features and so on. But when it is all added together, we are struggling to even identify the horses let alone the zebras.

### **Sean Sanders (host):**

*Obviously, there are clear challenges, especially in the low-and middle-income countries, and you are in the US, we have some advantages here, but what role do you see the primary care physicians playing in this, both in first world countries like the US and throughout the rest of the world as well?*

### **Eyby Leon Janampa:**

Primary care doctors have a very key role on identifying patients that can potentially have a genetic disorder. In the US, we have many patients referred to us just because there are some delays in development, not necessarily because the child looks different. We have a lot of patients that are healthy, growing well, and they just have the diagnosis of autism, for example. We try to do our best to give as much as testing possible, but there is, of course, challenges of insurance coverage and resources that the families have. We can, of course, diagnose clinically, many of the common syndromes. Many pediatricians follow patients with Down Syndrome, and not necessarily need a geneticist to take care of these patients. There are clinical guidelines that the American Academy of Pediatrics have reported many years ago, and it is very well known by the pediatricians in this country, in other countries as well, and is being followed. But of course, there is lack of training in other regions, or even in our centers, sometimes we see patients that have not been picked up by their pediatrician, but it is not as common as in other areas.

### **Durhane Wong-Rieger:**

Sean, if can jump in, because I think that what Helen was saying and what Eyby is referring to as well, your question around what about the role of the primary care and the pediatrician, I think it is huge because that is where parents go, that is where patients go, but unfortunately, as we say, when you are looking for a ze-

bra in a field of horses, especially if you are short of time, and you do not have quick diagnostics, that is our goal. I belong to several consortiums, one of which is Undiagnosed Diseases International, which is a huge international network, really focused on the undiagnosed. One of the most important groups out of that is the Blackswan Foundation (<https://www.blackswanfoundation.ch/en/>), which again, is a network of people without diagnosis, which is interesting because their only commonality is that they do not have a diagnosis.

The other thing I am a part of is the Global Commission on Ending the Diagnostic Odyssey, and I know that the Children's Hospital is playing a huge role in terms of trying to do that kind of networking. So, part of it, I think, is being able to not train pediatricians and general practitioners to recognize 6,000 rare diseases - that of course is impossible. In many cases, as they say, they will never see a specific rare disease, even some of the more common rare diseases. What we can do is give them better tools so they know in fact where to go if they do have a rare disease. And signs and symptoms, then they can have a portal that they can go to and look that up, and then they can refer to a specialist, including places such as Rady Childrens Hospital in San Diego.

We need to do a better job of then giving these frontline healthcare professionals the tools so that they can recognize that there may be more tools. We certainly understand the frustration of families and parents who try to tell their doctor that "my child actually has something wrong. And yes, you have given me a diagnosis, and you are giving me a horse diagnosis, but it is not working. And I am doing all this stuff, and it is not working." We need to also train the healthcare professionals and the pediatricians to listen to the families, but we also need to help the families to be able to better document what it is they are coming in with.

***"We need to also train the healthcare professionals and the pediatricians to listen to the families, but we also need to help the families to be able to better document what it is they are coming in with."***

I think it works on both sides of that, and I am really excited by some of these ini-

tiatives that are taking place that involve fancy genomic sequence that do a great deal for us but getting back to where it starts is also important: parents, patients, better understanding, better articulating. What I really want from the family physicians and the pediatrician is to listen, to pay attention, and then we need to have places like Eyby's, that says, "okay, we are not getting there, can you help us? Do we have a referral?" Or, the Undiagnosed Disease Network that says, "here are some guidelines. If you are seeing some of this stuff, then maybe you can refer to us." We do need to do a better job ourselves of being able to set up a network, so it is much better for that frontline physician, that pediatrician who is right there at the crosshairs, to be able to do their job, but it means all the other parts need to work as well.

*"We do need to do a better job ourselves of being able to set up a network, so it is much better for that frontline physician, that pediatrician who is right there at the crosshairs, to be able to do their job, but it means all the other parts need to work as well"*

**Sean Sanders (host):**

*The next part of the topic which I would like to talk about, is finding a solution. I think you have touched on some really critical issues there that we are going to definitely dig into, but maybe I will turn to Dong and just see if you have any comments and thoughts, particularly from your perspective in Asia.*

**Dong Dong:**

Yeah, I think Durhane was touching on some very important topics here. I will give you some examples. A few years ago, I was attending a conference in China about rare diseases, so one of the presenters was talking about neonatal screening panels. You can screen 30 or even 40 genetic diseases all at once, and these are provided for free by the government. The presenter was trying to show off these achievements, that now we can detect all these genetic disorders at once. It is efficient, and good news for the par-

ents. However, surprisingly, there was a very famous geneticist in China, he stood up, and he spoke critically against it. He said, "if you do not have any counter measures, if you do not have a very good social support system, how can you tell the parents that their newborns are having these genetic disorders?" Can you expect what these parents are going to do with the newborn? You do not have a very close bond with a newborn, and it is easy for some of the parents, especially if they are living in poverty, they do not know how to deal with these issues, and there is no social support, no social welfare system to help these parents to raise a child with this disease. The easy decision is to abandon the child. Without having any ethical or social considerations before taking this neonatal screening test, there is no test to be done.

*"When we are thinking about diagnosis, we are thinking that diagnosis is good for all the parents, for all the patients, for all the families. However, we do not consider enough the consequences brought up by this diagnosis."*

I was hugely shocked, but was enlightened by his insights and his perspective, simply because when we are thinking about diagnosis, we are thinking that diagnosis is good for all the parents, for all the patients, for all the families. However, we do not consider enough the consequences brought up by this diagnosis - are we ready, are we fully prepared to embrace this disease, do we have enough solutions after we get a diagnosis, can we find treatment for them if there is no medical treatment, do we have rehabilitation? Do we have other ways to help this family and this patient? When I was doing ethnographic studies in China, I went to the clinics and tried to observe the doctors and patients talking about their screening test results, you can see that everybody's reaction is so different. Some of the families, they got excited when they have a result, but some of the families, they just broke down when they know the results. They do not know how to deal with it, you can see, you can tell some of the couples are going to get divorced right after it, because if you are carrying a bad gene, I do not want you to have my child because this is going to be carried in my family.

Are we ready for getting a diagnosis? This is something that is a dilemma. I have no answers for that, but perhaps in the future, with better social care, with a better healthcare system with improved social support, we can have answers for that.

**Sean Sanders (host):**

*This is a very interesting topic, and it has come up in previous webinars. Clearly there is some controversy there. Helen, I will come to you now.*

**Helen Malherbe:**

Dong, you mentioned several very good points in there that I agree with, but at the same time, the power of having a diagnosis, even if there is no treatment available, or even if there is treatment available, but it is inaccessible in the context, it is so powerful. The family is under immense stress when you have a child with a rare disease, and just knowing one thing, at least what it is, enables you then to make informed choices about having other children. Is it a condition that could affect other children that you have? What is the prognosis? What is the treatment? What can you do practically? Because I think the most important thing about having a child with a rare disease, or a loved one with a rare disease, or yourself, is just not being in control and not being able to change it. At least if you know something, you can come to terms with it. Many people with rare diseases, or children with rare diseases, we do not celebrate, we remember those diagnosis days which are important dates on our calendar.

I think just a couple of other interesting points that have been raised here, we are in a situation here in South Africa, we do not have access to newborn screening. It is not available for many only a few of the population that can access private health care, which is only about 15-16% of the population. Even then, things like non-invasive prenatal testing, which is a screening that you can do for a lot of things like Down's Syndrome and so on, is not available here at all. So many of what is run-of-the-mill or standard practice in other countries, we do not even have available here yet, so the technology is moving along, but we are still where we are now. I think the other important issue, and this may also be an issue in China, Dong, is the whole matter of myths, the traditional beliefs in society and the stigma that is associated with patients with rare diseases, so whether they have a diagnosis or not, I can understand, in my context as well, where babies do get abandoned. In many cases in many of our communities, they

are hidden, the children are hidden, and they are only brought out in the middle of the night for treatment, so there are a lot of factors on this whole topic.

### **Durhane Wong-Rieger:**

I have two children, both born with rare diseases. My daughter never got a diagnosis, has never gotten diagnosis, she is in her 30s now. The first couple of years were extremely challenging because we did not know what she had. She had a lot of symptomology, we did not know if it is going to get better, or if it is going to get worse, but you do what you can, right? You do all the rehab process. We were lucky we live in Canada, we have excellent healthcare, so we had lots of resources. But of course, and I think today, if we were to go in, we could probably do a genome sequencing and probably identify what she might have, but that is up to her, she is an adult now so she can decide what she wants to do.

My son was born with a rare heart condition, needed diagnosis, knew exactly what it was, he had a prognosis, he had excellent milestone care up until he was 18, where our pediatric system ends and the adult system becomes a mess, but that is a different story altogether. So there is a huge difference between having a diagnosis or not. And sometimes you get a diagnosis, and it does not give you a prognosis, right? It does not tell you anything, but it does, as Helen says, it might tell you in terms of what the future might be, etcetera. You know, not having it. But I will say also, one supports the other. I mean, you look at Taiwan for instance, their rare disease community is huge. Hong Kong, the rare disease community is huge. Part of it is having that support network, but that support network does not come if you do not have a diagnosis and if parents do not get a diagnosis.

*“Part of it is having that support network, but that support network does not come if you do not have a diagnosis and if parents do not get a diagnosis.”*

In Canada, we do not have a standard, but we have it fairly good. Some of these diseases, and as we well know, if you take preventive action at birth, at the beginning, you can avoid a lifetime of actual symptoms or even early death. I remem-

ber having a conference in Asia Pacific and one of the geneticists. Let me share two very quick stories. One of the geneticists was asked the question, I think she was in Indonesia or Thailand, I cannot remember where. She was asked, “How do you decide, as a hospital, as a government, which diseases you should test for because there are limited resources?” And she said, “easy, we test for those diseases that we can do something about.” It is kind of your question, Dong. It is the case. Part of it is because the resources are limited, but the more we can test for rare diseases, the more we can stimulate getting something done about it.

*“The more we can test for rare diseases, the more we can stimulate getting something done about it.”*

I think that is an important thing. Newborn screening is something that it should just be a standard. We need to have an international summit on newborn screening, these things are cheap, for the most part. And she said, we can do panels that can do 25, 50, 60 diseases at once. It is a blind spot, right? I remember hearing a story from the geneticist in the Philippines who has made it her mission to do newborn screening for her patients. She was telling the story, it was the middle of a monsoon. She says, “You know, we have hundreds of islands and what we do is we collect these newborns’ blood smears. Then we bundle them together, and we deliver them. I had a bundle of tests that was coming, I have a monsoon, and I am desperate, because I must get these tests to get these results, to get them tested.” They got the navy, they got fire departments, they got police to hand the bundle, from island to island. “And we got the tests, and we got the results. That is how important it is for us to get those newborn screenings.”

I think we need to, as a global community do what we can do for newborn screening. It is a must; we have got to get this.

### **Helen Malherbe:**

I agree completely Durhane. But our issue is that we have so many competing health challenges. We have got ongoing infectious diseases, we have malaria, plus South Africa is one of the hardest hit countries in terms of HIV. And along with that, comes TB. And so these diseases get the lion’s share of resources.

And obviously, in those cases, if there is a comorbidity, where you have got someone that has an infectious disease and a rare disease, often the rare disease will get missed and then only the infectious disease will get diagnosed. Or, we have a lot of cases where there is a misdiagnosis, and in cases where it is life threatening, it never gets recorded. And it just, it is a negative cycle, because we need to create and demonstrate the case. We must have the evidence to show that rare diseases and congenital disorders are a problem, so that can inform our policymakers, so we can get that political commitment and allocate the funding. But we are fighting with and competing with so many other health priorities.

*“We must have the evidence to show that rare diseases and congenital disorders are a problem, so that can inform our policymakers, so we can get that political commitment and allocate the funding. But we are fighting with and competing with so many other health priorities.”*

### **Eyby Leon Janampa:**

I think it is very important to educate not only the providers, but also the general population. In the US, even though it may be, standard of care to do the newborn screening, there are families that do not want to get the newborn screening, because they think that you can clone their baby with a blood spot. In this country there is still some skepticism about doing any type of testing that involves blood or even DNA sometimes just because you want to screen a baby. And so, the training for primary care providers is very key, again, just because many babies or patients that, for example, you are treating for an infection, you give all the standard therapy, but the baby does not get better, it is maybe a metabolic disorder. But again, the challenges of how expensive is the treatment? Or the efficacy of a treatment.

There are private companies that push countries to screen for conditions where treatment is so expensive, and it is not that efficacious to improve quality of life, too, like the lysosomal storage disorders. In countries like in Brazil, where sometimes the availability for treatment is not

possible. But, I think to give a diagnosis, regardless of the resources available, will be ideal. But of course, I think education should be first, not only for the primary care but also the population. I think it will be the most important thing before expanding all types of DNA testing because there is a lot of what Dong said, skepticism and misconception about what we can do with these results.

*“We assume that the health-care resources are equitable, like everybody can get equal access to all these health care resources, but it is not the case.”*

### Dong Dong:

We have some assumptions here. We assume that the healthcare resources are equitable, like everybody can get equal access to all these health care resources, but it is not the case. It is not just at a global level but within the country or even within one city. So, if one parent or, one family, get a diagnosis on the baby, and if the baby living in a wealthy family, so definitely he or she can get enough support. Even if s/he lives in Canada, or in other countries who have very good health care systems, the support is mostly free, so the family can get support.

In China, which is a big country, we also have lots of issues. Rare disease is not the top of the list of the healthcare issues that we want to deal with. So, in China there are lots of discussions as to whether we should use national healthcare insurance to cover the treatment and diagnosis cost for rare disease patients. There is push back from the public and from experts. They are saying that we have so many common diseases like cancer, and Crohn's disease, that we need to deal with. If it is based on an equalized basis, everybody can share just one slice from this big pie, this big healthcare insurance system. For rare disease patients, lots of the treatments are expensive and lifelong, and the effectiveness cannot be measured using the traditional economic ways of doing it. It is not cost-effective. That is why you should not take the same slice of the pie or even bigger slice of the pie from the National Healthcare System. That means nobody is trying to support rare disease patients. They are not doing anything based on health equity or, the concept of health equity. They are functioning

based on the concept of health equalization. We are proposing that rare disease patients have different needs, if they want to raise their quality of life, if they want to have a good treatment, and if they are going to have all this expensive treatment. They are going to take a bigger piece of the pie from this national healthcare insurance. If you cannot allow people to do that, then how can we talk about giving everybody a diagnosis and the treatment, there are no available resources.

### Durhane Wong-Rieger:

Huge advances in terms of understanding and research are not going to happen unless we actually invest. I see rare diseases and many other diseases as well as an investment, what can we do here? We are investing in the patient, we are investing in the family, we are investing in research, we are investing in new treatments, because if we do not do it, then we are always going to be stuck in the same spot, and we are not going to be able to advance.

China, quite frankly, has a vibrant rare disease community, doing some of the best work in terms of genomics. If look at gene therapies, we have advanced to the point where we can cure some of these diseases. That will have a huge impact. “Should we go into space when there are so many other needs,” Somebody asked Jeff Bezos.” He said, “These are things we invest in because there is a future here.” What we are going to learn from genome sequencing and gene therapy is going to help. At some point we are going to cure cancer, and we are going to cure some of these genetic diseases using some of what we have learned from rare diseases.

### Sean Sanders (host):

*Let me ask, just related to this, how do we empower patients and their families to advocate: to the government, to their local government, to their doctors.*

### Eyby Leon Janampa:

Parents especially, are very driven to promote research in rare disorders. In my center, we see families where they want to not only create support groups, but also promote research that will deal with potential therapies for rare disorders. There have been more and more groups where they have been able to create animal models just through funding with a social media and being able to get a better understanding of the pathways that are affected with these mutations or changes in the DNA that cause the disorders. Genetic testing often is available to many of

the families that we see in the center, and we are, almost every few months, getting new diagnosis of very rare disorders where only a couple of patients have been reported, and the parents are already looking for more answers.

There is a national organization of rare disorders in this country that is trying to help these families for them to own their own data, so they can share this information to several entities instead of, for example, a pharmaceutical company using this data for profit only, and not able to share or not wanting to share this data to other potential companies that can invest for research and treatment. I think that is very key because we already have problems with other not so rare disorders that have treatments, current treatments, for example, lysosomal disorders, where different companies own data of different diseases that belong to the same pathway, and they do not share that information. And they have this humongous data that yes, they will publish, some of it but not all, and it will delay potential treatments for the future that will benefit these families.

### Sean Sanders (host):

*Something I wanted to touch on in the last quarter of this webinar is looking to the future, where do we go from here? Durhane, earlier, raised several important pathways I think that we could follow. The first question I had, and Durhane, maybe I will come to you to answer this one, is what are some of the unique advantages that a general practitioner or a primary care physician, or family physician has in diagnosing a rare condition? Also, what are some of the unique challenges that they might face in low and middle-income countries where they maybe do not have the resources to do the testing that they would like to do?*

### Durhane Wong-Rieger:

I am very sensitive to what Dong said, and that is, we test and we identify a disease but do we have the resources? Do we have the support to send this family to the doctor needed? I think this is true in many, many countries. The family physician, the general practitioner is in fact that focal point, so we have got to do a better job of empowering them. Somebody said to me, “90% of the time,” he says, “we can identify a disease by symptoms- if I know enough about symptoms, . I do not need to go to the fancy stuff yet [e.g. genetic

testing].” So that is very interesting but of course, the challenge is, can we really explain 6,000 diseases to a GP and say, “Okay, you might come across one of this. You are going to spin the rolodex, and it is going to come up.”

In the age of internet and digital, and AI, we are developing some of these very amazing portals where you can actually enter symptoms, and it begins to guess what the condition might be. You get to a point where it says, “Okay, we think it is this, this, and this.” And then, you can begin to also do a little bit of your own research and be able then make a referral. But that also presumes that you have got a physician who not only cares, but has the time and the resources to do that. Not everybody is in a position where they can say, “okay, I have got hundreds of patients, and I am going to take the time it requires to actually diagnose a rare disease patient.” It is easy for the families to get frustrated and say, “you are not hearing me, you are not listening to me, you are not following up on me.” The poor physician is beleaguered because they have got tons of other patients that they could probably easily treat within that same period.

***“The poor physician is beleaguered because they have got tons of other patients that they could probably easily treat within that same period.”***

It is also getting people the right tools. I think we need more centers like the Children’s Hospital where it becomes a referral site, and where they are better resourced to take these referrals and they can be the specialists. We have a new thing that we are trying to talk about - how do we train a network of maybe GPs and pediatricians to become rare disease specialists? The same as we have cancer specialists in the GP community. We have them especially more in Canada. We think about people who live in northern communities; where they do not have access to centers, and specialists, can we train you up to become somewhat of a specialist? We then can link you, electronically, to a major center where you can get the support. European centers or reference networks are like that.

Under RDI, we have a concept of creating with the WHO what we call a Collaborative Global Network for Rare Diseases

- creating a global community of rare disease centers of excellence and being able to network them so that they can service resources. If you are far away from any major center, that you can access the right specialist. That is a big goal. It is a 10-year goal, it could be a 20-year goal, but that to me, that is the way we can empower a family and physician on the front lines to access the right kinds of specialists to make that happen.

Where does the care and support come from? It comes from an international community that hopefully, with a great deal of technology, people can tap into. It is a vision, it is a long way out, it is going to take a lot of resourcing, and not just from each country’s own public system but it is going to take a lot of private support as well, but that is the goal.

#### **Dong Dong:**

I agree with everything you said but I want to play the devil’s advocate here a little bit. Because I really do not think we should overburden the primary care system. Rare-disease diagnosis requires lots of specialties and lots of trainings in multi-disciplinary areas. Many rare diseases do not belong to one particular discipline. Rare disease patients need doctors and specialists from different areas. They can work together and coordinate, then provide a diagnosis. For the primary care system, for the GPs and the family medicine, they do not have, and we should not ask them to have this kind of training. That is not fair for them because their job is to take care of the public. How can you ask these doctors to spend years of years of training feeling like they are failing themselves for not being able to diagnose rare diseases?

#### **Durhane Wong-Rieger:**

It is the opposite of what I was saying, Dong, and that is, they do not do the years and years of training. They do enough to understand that the patient may have a rare disease and in what area that rare disease might be. If I can give you easier access to the information that says, “okay, now I need to refer you over to here,” or to multiple centers. The goal is to take the burden off the front line. I agree with you totally, it is not up to the primary doctor to reach that diagnosis. They should not be burdened with the diagnosis, but they should be able to know and have places where they can refer the patients to, the same as they can do a deep diagnosis of cancer. We do not expect them to do that, we expect them to be able to refer it over. So that is what we do not have, is “Where am I going to refer these patients to?”

***“That is what we do not have, is “Where am I going to refer these patients to?”***

#### **Dong Dong:**

Based on China’s experience, one of the reasons why Chinese patients can get a diagnosis very efficiently is because of this uneven distribution of healthcare resources. It is amazing. When you think about uneven distribution of healthcare resources, we may think this is a barrier for people to get diagnosis, but, it is not. Because whenever a patient cannot get a diagnosis at the local level, like from the community hospital, they just fly to Beijing or Shanghai, big cities, with the best hospitals in the country, then boom! They get a diagnosis immediately. So that is why the whole diagnostic journey is so short in China just because of this uneven distribution of medical resources. It sounds ridiculous, but in a sense, it also tells us that we should not totally rely on the primary care system. We should let people understand that diagnosis of rare disease is not just one person’s responsibility. It requires lots of support from the entire medical community.

That is also why, in China, they are trying to do teleconferences and teletraining courses centering on these big hospitals. Such as Peking Union College Hospitals in Beijing, one of the best hospitals, and they train the doctors at the local level in the community hospitals, try to let them have a common sense of what rare disease is. Then, they establish this network, so whenever those doctors at the primary care system they see something peculiar, something strange, they will refer them immediately to those doctors who have this capacity, who has this ability to give a correct diagnosis. I truly believe this is a more efficient way, and this is one of the best way for patients to get a diagnosis.

***“Whenever those doctors at the primary care system they see something peculiar, something strange, they will refer them immediately to those doctors who have this capacity, who has this ability to give a correct diagnosis.”***

**Sean Sanders (host):**

*Helen, I am very interested to hear your thoughts on the position in South Africa.*

**Helen Malherbe:**

I think, ultimately, it comes down to education and advocacy at all levels, whether it be the GP or the MD in the hospital. You must remember, in South Africa, the primary healthcare setting, a lot of the time, a patient is seeing nurses, so you need to build up the curriculum for genetics at nursing college. The first line of nurses will then know when they need to refer to a doctor, and then up through the referral network that we have here in South Africa. I think knowing when to refer to is so crucial and so key. It is very interesting listening to colleagues from around the world because, obviously, every country is in a unique situation. I have painted a rather negative picture, in some respects, for South Africa, but there is so much happening here because advocacy is ongoing at so many levels and education is happening at so many levels. For example, we are now developing a rare disease strategy for the country, which is exciting, and we are involving all the different stakeholders and then have that strategy recognized by government.

*"I think knowing when to refer to is so crucial and so key."*

We are presenting at one of the portfolio committees next week on our input into the National Health Initiative in South Africa, which is essentially a funding mechanism for universal healthcare here in South Africa. Of course, it has been blown out of the water by the required COVID response, and so all the funding has been re-allocated to COVID. But nevertheless, we have got a universal healthcare approach there that is gradually being implemented. There is resistance, yes, it is slow, but it is there. We have been able to comment on that and feed into that process, which is where we are headed next week to government. We also have a human genetics policy that is being revised here in South Africa and we have some great policies and laws, but implementation is where we are falling short, and it does come down to resources. That brings me back again

to advocacy, education, awareness at all levels, whether it is talking amongst patients, patient support groups, clinicians, nurses, government, policy makers, researchers, whoever. There is a need at all levels and every sphere for improved education and advocacy.

*"There is a need at all levels and every sphere for improved education and advocacy."*

**Sean Sanders (host):**

*Something that both you, Helen and Dong, also touched on is this hidden population, which I think is really critical, and it is not something we have talked about in previous webinars, but I think finding that population, getting to them, diagnosing, detecting rare diseases, and then being able to treat them is really critical. With that in mind, for the last few minutes, I wanted to talk about what needs to change in the next decade or two. This is a marathon, it is not a sprint, it is going to take a long time to change things, so what do we need to move things forward?*

**Helen Malherbe:**

From my perspective we need evidence for South Africa. Our health system is evidence-based, and it will only take notice if we have the data; if we have the published research and, if we have that expert knowledge from rare disease patients themselves, As a collective, it will become a cacophony but the government will have to have to listen to and will hopefully make an impact in the same way that HIV activists actually got HIV on the agenda here in South Africa.

education is very important for not only the medical care providers, but also for the general population.

**Eyby Leon Janampa:**

I think education is very important for not only the medical care providers, but also for the general population. So many times, families come to us with a diagnosis because they found it on Google. I think a better policy is to have rules, very clear rules of data and how to share that data from laboratories. We should have,

by now, a better system where we can share all the information worldwide. There are little steps that the American Academy of Genetics are trying to do, but we are way behind based on the technology that is available, so we need to catch up. The only way, I think, to go forward is to share it internationally with everybody.

*"Better policy is to have rules, very clear rules of data and how to share that data from laboratories. We should have, by now, a better system where we can share all the information worldwide."*

**Durhane Wong-Rieger:**

I will pick up on two things. One is that we need the evidence. I think we need the evidence, and we need economic evidence. I asked Samuel Wiafe, who runs the Rare Disease Initiative, Ghana, "How did you get the government to pay attention, to begin to introduce newborn screening, to actually have training, and how do you get your colleagues on board to actually treat rare diseases?" The answer was by collecting evidence and collecting the data. Some of that was very simple, for example to show how many patients were ending up in hospital with rare diseases that were not diagnosed, and who could have avoided the hospital if we had diagnosed them. That was collecting that evidence. It does not have to be big, high-powered data. What does rare disease care cost? What would be the benefit? I think we need to do a good job of being able to collect the evidence and turn it into economic data.

I think we need to do a good job of being able to collect the evidence and turn it into economic data.

The second thing that I will say is I think we need to work together as a global community. Rare Disease International is introducing a resolution at the United Nations. It is a resolution to recognize rare diseases because it is not just a healthcare issue; it is a social issue, it is an equity issue, it is an education issue, it is a women's issue, and it has a huge impact. The United Nations included rare diseases in universal health coverage a couple of years ago, we fought very hard for that, and it really was part of what we felt was an important message and that is, leave no one behind.

*“Rare diseases ... is not just a healthcare issue; it is a social issue, it is an equity issue, it is an education issue, it is a women’s issue, and it has a huge impact....leave no one behind.”*

Just because you have a disease that is representative of a very small number, it does not mean you should be ignored. You have as much of a right to get access to healthcare and to be treated and supported, familywise, etcetera, as anybody else. But secondly, by working together, there are many common solutions for rare diseases. It is not as if I have to take each and every one of these 6,000 diseases and come up with a unique pathway for diagnosis and treatment. We know that is not the case. 80% of them are genetic. There are lots of things that can be done in common. It is the same with cancers - we think about them collectively, 6,000 or 7,000, and we have many commonalities in that strategy and many of those strategies will work across the globe. These strategies will also work only if we take global action. I am very excited about opportunities like this where you hear what other countries and other specialists are doing. We need to continue to forge that global alliance in looking for solutions.

We need to have transborder and transdisciplinary, transracial, even transglobal collaborations.

### Dong Dong:

When I was thinking about this question, I thought about several keywords. The first word is “trans”. We need to have transborder and transdisciplinary, transracial, even transglobal collaborations. We also need to break down the walls. There are lots of walls built up in the past few years at different levels, so we need to tear those walls down and try to get connected. We need to share; share information, share our knowledge, but also share our life stories, share our experiences, the tears and loss, among the community. We need to have belief in these patient communities. I have seen in the last several years, how creative they can be, how strategic they can be, how vibrant they can be. Patient communities can find out different ways to empower themselves and to enlighten others.

*“We need to share; share information, share our knowledge, but also share our life stories, share our experiences, the tears and loss, among the community. We need to have belief in these patient communities.”*

The last thing I want to share with you is a doctor’s note about rare disease from a few years ago. He was proposing that we should not say the disease is rare or not because when we are trying to label rare diseases as rare, no doctors will think that they are going to encounter any of this disease in their lifetime because they are rare, so we should not emphasize on this concept anymore. We shall let people know that no disease is rare, every disease can be common, and you are and you will encounter these rare cases in your life, so get prepared. Everybody needs to think about there is no such thing as rare in our life. In that way, we can help people to better understand all these diseases, all these difficulties that human beings, human society is facing right now, so that we can work together trying to deal with it.

Everybody needs to think about there is no such thing as rare in our life. In that way, we can help people to better understand all these diseases, all these difficulties that human beings, human society is facing right now, so that we can work together trying to deal with it.

### Sean Sanders (host):

*If you would like to send us your thoughts on today’s webinar, please email [webinar@aaas.org](mailto:webinar@aaas.org). Thank you.*

## Journal Club

### Article of the month

**Value based healthcare for rare diseases: efficiency, efficacy, equity.**

**Fantini B, Vaccaro CM. Value based healthcare for rare diseases: efficiency, efficacy, equity. Ann Ist Super Sanita. 2019 Jul-Sep;55(3):251-257. doi: 10.4415/ANN\_19\_03\_10. PMID: 31553319. <https://pubmed.ncbi.nlm.nih.gov/31553319/>**

We here today in our webinar that patients with rare disease have the right to a diagnosis and healthcare. However, the healthcare system is not well prepared for rare diseases. There are many misconceptions and misunderstandings. Also, many doctors are not familiar with rare diseases and how to diagnose them. This article, “underlines the necessity of new culture of health and well-being, radically re-examining how to organise the delivery of prevention, and healthcare services, and finding alternative ways of empowering and giving voice to vulnerable and marginalised groups.”

## History Corner

**Ancient wisdom, modern practices: A brief overview of healthcare practices in Ancient Greece**  
by Florian Delval

**The popular expression “healthy mind in a healthy body” perfectly reflects the ancient Greeks’ views on healthcare and medicine. For Hippocrates and his Kos School of Medicine, establishing good healthcare practices was a focal point for which the master and his disciples designed clear procedures. Hippocrates was the first to apply a global vision to medicine, focusing on the method, examination, treatment, prognosis, and diagnosis, as well as the promotion of what he considered healthy behaviours.**

In ancient Greece, balancing the body and the mind was essential. For the Greeks, a person with a developed and balanced body and intellect was someone to be valued. This notion is also reflected in Hippocrates’ natural approach to diseases. At the time, physicians also believed that physical and mental health were interconnected. Hippocrates was indeed the first to consider his patients in a holistic way, focusing on body, mind, spirit, and emotions. He considered, amongst other factors, that environmental causes, psychological factors, nutrition, and lifestyle all needed to be taken into account

while examining a patient. This innovative outlook established a better approach to health care practices, enabling physicians to better diagnose, treat and prevent diseases. For Hippocrates, knowledge and observation thus created a better differentiation of diseases, permitting physicians to make accurate diagnosis.

In order to be as accurate as possible, Hippocrates' disciples relied on a clear methodology, based on observation and collection of information from the patient. From 5<sup>th</sup> Century BC, Greek physicians started to consider geographical location, climate, age, gender, habits, and diet in order to help them make a proper diagnosis. They also took notes of mood swings, sleep duration, dreams, appetite, severity of pain, convulsions, nosebleeds, and many other characteristics that might explain a disease. This scientific reasoning and approach also relied heavily on experience, not only to make an accurate diagnosis, but also to make an evidence-based prognosis and therefore select the most adequate treatment. According to Mark Schiefsky, author of *Hippocrates On Ancient Medicine: Translated with Introduction and Commentary*, published in 2005, the core of Hippocratic medicine was based on "the precision or the details of prognosis and the reliability of prognostic signs."

Hippocrates and his Kos School of Medicine were also the first to consider psychological and mental illness as common afflictions. The approach was therefore the same as for physical illnesses. Hippocrates believed that, for instance, the brain was the organ responsible for mental illness. In this context, the role of music and theatre in the treatment of illnesses was used as early as 2,500 years ago. It was a novel and innovative approach that was applied for both diseases of the soul and body. Ioanna Papatheanasiou, co-author of the article *Health care practices in ancient Greece: the Hippocratic ideal*, stipulates that "there were specific musical applications for certain diseases. For instance, the alternating sound of the flute and harp served as a treatment for gout". For people who were struck with *mania*, mental illness, what we could define as "quiet rooms" were also designed. Their aim was to allow the patient to sleep better, ultimately improving their mental health.

In addition, the importance of physical activity was also understood as a way to treat certain diseases, but also as a way in which to prevent them. Sport was often used to optimize functional capacity, but also to help rehabilitate the injured or disabled. Sports competitions in ancient

Greece were a leading and popular activity, which in certain cases made it possible to overcome a physical disability. For example, Egyptian Mys, who compensated atrophy of the arm by practicing sports. He eventually became a renowned wrestler. Or Pyron of Helida, who fought his dystrophy contracted during childhood by devoting himself to physical activity and focusing on the pentathlon. He eventually managed to win the Olympic Games. For Hippocrates, physical exertion of maintaining good health and physical fitness was about physical education, while the use of exercise for therapeutic purposes concerned medicine. The *Paidotriyai* is also an important specialist of note. These specialists' role was to accompany athletes during the Olympic Games and prevent them from injury. For instance, they used olive oil to warm up the muscles and increase body temperature. It is still widely used today. An emphasis was also made on nutrition. The consumption of glucose concentrated fruits, such as figs, was recommended to boost an athlete's energy and increase performance.

**Spanning back beyond 2,500 years ago, practices still considered innovative today were already in use. The legacy of Hippocrates and his Kos School of Medicine is even more impressive as it came from a world where medicine was strongly influenced by divine beliefs. They were the first to transform it into a rational, evidence-based discipline. Today, it is easy to observe Hippocrates' influence since we owe him many terms still used in medicine today, i.e. diabetes, cancer, coma, paralysis, and epilepsy. Hippocrates was also the first to establish an ethical framework for the practice of medicine, highlighting integrity, benevolence, and human dignity. It is quite sobering to realize how much Hippocratic medicine has influenced medicine to this day.**

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## What's up?

### Highlights of the month

#### Movies to move you by Morgan Packer

A diagnostic odyssey, whether for common diseases or rare disease detection, can be trying on families and on those afflicted with an illness. This scenario is one certainly familiar to the big screen, but a few TV shows and movies stand out. Here are some of my personal favorites:

1. An all-time award-winning series, ***House, M.D.*** (2004-2012), follows Dr Gregory House (played by Hugh Laurie) and his eccentric, frequently unconventional ways to diagnose patients. Walking away after 8 seasons with two Golden Globe awards and five Primetime Emmy Awards, House is one of the worlds' most watched TV series in history.
2. Eerily relevant to the global reaction initially caused by Covid-19 in early 2020, the movie ***Contagion*** (2011) directed by Steven Soderbergh follows the attempts of WHO and CDC officials to identify, treat, and contain a new virus, known as MEV-1.
3. A recent Netflix series, ***Diagnosis*** (2019), takes inspiration from a chronicle article in the New York Times to accompany Dr Lisa Sanders in seeking answers on behalf of patients for their undiagnosed diseases. This series provides useful insight into what diagnostic wanderings mean for patients and their families.

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