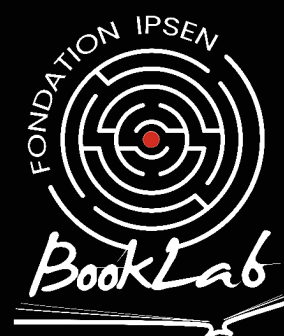


The Rare Disease Gazette

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

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**MIND
MATTERS**



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

Kathleen Bogart, PhD (Oregon State University, Corvallis, Oregon)

Amy Hunter, PhD (Genetic Alliance UK, London, UK)

Sean Sanders, PhD (Science/AAAS, Washington, DC)

Debra Regier, MD, PhD (Children's National Hospital, Washington, DC)

Kym Winter (Rareminds, St. Albans, UK)

Sean Sanders (host):

In this nine-part series, running through the remainder of 2021, we are looking at some of the most critical issues in the field of rare diseases. If you would like to watch previous webinars in the series, you can find them at webinar.sciencemag.org.

We have already covered many different topics related to rare diseases, including the challenges of diagnosing and detecting rare diseases, the role of primary care doctors in this process, pros and cons of neonatal testing, and application of artificial intelligence in rare disease detection, diagnosis, and research. Today, we are shifting gears from physical to the mental to address psychological impacts of rare disease, and the importance of not neglecting the mind-body connection.

I am very excited to introduce our panelists to you; welcome, to all of you. Thank you for joining us. As usual, I am going to have each of you introduce yourselves and tell us a little bit about what you do. So maybe we will start with Dr. Kathleen Bogart. Kathleen, please go ahead.

Kathleen Bogart:

I am an Associate Professor at Oregon State University here in America. My interest really is squarely in quality of life and psychological support for people with rare diseases. I was born with a rare disease myself, and I am very interested and motivated to serve my community, and to provide additional support. I have done some of the largest quality-of-life studies

of people with diverse rare disorders, and I am happy to chat with you all today and learn more about what everyone is up to.

Sean Sanders (host):

Thank you so much, Kathleen. Next, we have Dr. Debra Regier.

Debra Regier:

I am in Washington, DC, and I am the Medical Director for the Rare Disease Institute at Children's National. My work is around how do we educate to improve quality of life for all patients and families with rare disease, whether through the diagnostic odyssey or once they have a diagnosis. I am also the Director of the Palliative Care Genetics Clinic here at Children's National, which is a combination of doing palliative care, as well as understanding the genetic ideology for end-of-life or those individuals who have a short expectation of life. So again, it is all about how we optimize every day, and we realize more and more, mental health is a huge component of that. I am excited to be here today and discuss how to move things forward for our families.

Sean Sanders (host):

Thank you so much, Debra. Next is Dr. Amy Hunter, who is the first in our UK contingent. Amy, over to you.

Amy Hunter:

I am Amy Hunter based in the UK. I work for a UK-based patient organization called Genetic Alliance UK. We are a national policy organization, so our members, rather than being individuals, are largely small condition-specific rare disease patient groups. We work to give them a voice at a national level in the UK, and we do a lot of work to support them in their development as organizations. I am the Director of Research at the organization. The kind of research that we do is really focused on patient experience, especially around healthcare under the services, and then we draw the evidence base together to feed into our policy work to try to improve things. Through that kind of work, and through our interactions with our members, we hear a lot about the burdens of living with a rare disease in terms of mental health. We carried out a survey and an interview study a few years ago that uncovered a huge unmet need for better mental health support.

Sean Sanders (host):

Thank you so much. Finally, we have Kym Winter, who is also in the UK.

Kym Winter:

Thanks, Sean. I am Kym Winter and I am a Psychoanalytic Psychotherapist by background. I have been working for about 25 years as a therapist but became involved with the rare disease community professionally in 2014. Really, in recognition of how little support there was being offered to rare disease communities and individuals. Wanting to change that, started an organization, which is a nonprofit called Rareminds CIC last year. Rareminds CIC is working with patient organizations and health care professionals to both provide mental health services online and by telephone, because we recognize that one of the things is a difficulty in access and getting to appointments for rare disease patients and family members. But, also to raise awareness in the very way that we are, today in this webinar, really of how mental health is absolutely key to your physical healthcare, too.

Sean Sanders (host):

Before we sort of dig into the mental health side of things, I really wanted to just touch on some of the unique challenges that are encountered by people with rare diseases. Maybe we could just talk about some of those? We have covered them in previous webinars, but I think it is important just to lay the foundation. Kathleen, maybe I will come to you first. Could you talk about some of the issues that are unique to rare disease patients?

Kathleen Bogart:

Maybe I can start with things that are common to people with other chronic diseases, and then move on to what makes them unique. So rare disorders often affect multiple organ systems, are treated by numerous specialists, not just a single provider. And they are paired with the unique challenge of lack of information, lack of a roadmap of what someone's care or life would look like. And so that is really what makes it extra challenging. We already know that living with a common chronic condition is quite challenging, but some of the additional issues faced by those with rare conditions, are finding community, finding people who have had other experiences like them, and really finding those

doctors and specialists who know about the condition and even know what to look for during that diagnostic odyssey. During all of that, there are a lot of experiences of maybe invalidation or disbelief towards the individual with the rare disorder. Maybe it is all in their head if nothing is being found. And it can really affect someone's sense of hope and optimism.

Sean Sanders (host):

Debra, maybe I can have you jump in since you do work with rare disease patients.

Debra Regier:

Actually, as you were speaking, Dr. Bogart, the thing that came to my mind is, so often in medicine, we prioritize the medical concern, the organ system. There are liver issues or there is a kidney issue, and that is going to trump the priority list. Often, I will sit with families and say, "Okay, we need to see 12 specialists. Who are we going to see for one through 12?" Sadly, when I first started in this career, mental health never made it to the top 10, and thankfully, now I have learned, and now it does. I think it is a matter of how we prioritize our time and energy and resources. And I think, sadly, a lot of people in rare disease have been prioritizing it inappropriately. Now we know the better we can prioritize our mental health, the more likely we can handle all those other issues. But that is something that has just come into this field, and we are acknowledging that that is a huge component of every rare disease.

"Physicians are really good at, "This is the organ system. This is the test I need to send. This is the screen I need to do." Those are the easy things for us to deal with. Sometimes, it can be really hard to deal with, "Okay, I need to find you a therapist."

I think as you said that, that complexity, physicians are really good at, "This is the organ system. This is the test I need to send. This is the screen I need to do." Those are the easy things for us to deal with. Sometimes, it can be hard to deal with, "Okay, I need to find you a therapist. That is a harder thing for me to do. I need to find a good connection. I need to find you a community," which, that is a really hard thing to do, is to find community, sometimes. I think, exactly what you said, Dr. Bogart, it is so true. How do we, in the middle of this medical milieu, make sure that we do not forget that mental health is one of those components that we always have to bring in?

"How do we, in the middle of this medical milieu, make sure that we do not forget that mental health is one of those components that we always have to bring in?"

Amy Hunter:

I think that touches on something very important, when she said that there is this list of specialists that you need to start seeing. In the UK, we find has a huge impact on people's emotional well-being because it seems to be a real struggle for that care to be coordinated effectively. And certainly, over here, the burden of that tends to fall on the individual or the family, the parent, so there is a lot of chasing of appointments. There is obviously going to be a lot of taking time off work, taking your child out to school. Sometimes, you have two appointments in two different hospitals on the same day, because people are not talking to each other. Or conversely, you have got two appointments three days apart in the same hospital. It would have been a lot better for everyone if they could be at the same place. And I think when you throw into that mix, when you have got so many health care professionals involved, if they are not speaking to each other, as well, and they are just dealing with their little angle, whichever medical angle they are specialized in, then you can get to the point of the individual losing trust in their care. We do see that a lot, because when you lack that joined-up thinking, then mistakes are made, there are gaps and people feel like the care they are receiving is not of good quality overall.

"When you lack that joined-up thinking, then mistakes are made, there are gaps and people feel like the care they are receiving is not of good quality overall."

Kym Winter:

One of the things we hear a lot with patients who access our services as therapists is that they might have tried to access therapy before, but either they found their way to someone who did not have much understanding of the complexity of rare disease, and so there might have been a tendency to, what I would call, sort of over-pathologize their symptoms again, or look, as Kathleen was saying, to, "Is this really a physical symptom or is it actually an emotional one?" That very complex interface between physical and emotional. But I do not know how it is in the States, but in the UK, patients are managing a lot of appointments and doing a lot of juggling of their care. Now, if you add into the mix that it might be helpful to see a psychologist or a therapist, it is another appointment to manage. That appointment gets missed, and then someone might send a follow-up letter, but you might have to re-refer, or the psychologist or therapist might think, "Well, they are not motivated. It is not the right service for them right now." I think historically, it has been difficult for people to access the right therapy or psychology services. You add funding issues into that, as well, and it is a perfect storm; that is why it is hard to get there.

"If you add into the mix that it might be helpful to see a psychologist or a therapist, it is another appointment to manage.... historically, it has been difficult for people to access the right therapy or psychology services."

Debra Regier:

I am going to comment about the US; we have the exact same issues. We have the same issues with coordination of care. It sounds great in the US. We have all these resources, but coordination of care still falls to the parents, or the families, and the family and the patient. The other issue that we have is, depending on the type of insurance or healthcare system that the patient is in, they may or may not have access to very good mental health support. They might not have access to a therapist that is covered. This can get very, very expensive for families. And for example, my favorite therapist in the area does not accept any insurance, so it is all out-of-pocket cost for families, for my favorite rare disease therapist in the area. There are a lot of access issues that we can all share in understanding and thinking about how do we improve access, no matter where you live.? We all need to think about that as being a priority.

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Kathleen Bogart:

I think one other challenging thing about being in the US is the great distance that we encompass. Right? I have spent some time in the UK, while rare disease patients in the UK may have to travel a few hours by train to get to an appointment. It is very common in the US, if you want to see the couple of eminent people in your rare disease, that you may have to fly from coast to coast for seven hours. So, add that on to everything else. The really important point about mental health care and payment is that in the US, very few mental health providers are familiar with rare diseases. In fact, to my knowledge, there is no special training available to focus on [mental health in] rare diseases. The closest you would get would be a health psychologist or a health social worker who has some broad training in working with chronic diseases.

“To my knowledge, there is no special training available to focus on [mental health in] rare diseases.”

Kathleen Bogart:

There is something so unique about being rare that most healthcare or most mental health providers will not have experience with unless they have worked with a lot of clients. And that is why I think about have Deb's favorite person working in that space; you may have to fly or travel to really get to that space. With the pandemic we have been able to connect more with telemedicine. Maybe if you do not need a physical examination, you can Zoom to be with your provider – especially a mental health care provider - who would otherwise be across the country.

“A lot of mental health care professionals are quite frightened of rare disease. we have patients on our books who have said to us, “Well, I tried to approach someone, and they said, ‘Oh, I am not very familiar with rare diseases.””

Kym Winter:

You are quite right. And it is one of the ways in which it has become more acceptable and easier to access all different sorts of care, really. A lot of mental health care professionals are quite frightened of rare disease. I do not know if it is quite the same in physical healthcare, but that idea of “Do no harm” translates over into the mental healthcare field. We have patients on our books who have said to us, “Well, I tried to approach someone, and they said, ‘Oh, I am not very familiar with rare diseases,” or they do not fit under a service we mentioned. The NHS (National Health Service in the UK) is very stretched; if someone is slightly off to one side, as rare diseases often are, there is the feeling of, “Well, maybe we cannot quite bring

them under our umbrella of services.” I think more training and more awareness for mental healthcare professionals quite widely would be helpful.

We are a small organization. We cannot support everyone's rare disease mental healthcare. Getting that awareness out there and giving people confidence to understand just a bit more about rare diseases generally, even if the specifics are something that patients will work on with their therapist or counselor over time. But I think things are changing and I think there is more openness to both using telemedicine and mental health issues generally being talked about because of the pandemic.

Sean Sanders (host):

We have touched on lot of very different parts of this issue. We talked about funding. We talked about the complexity issue, which does seem to be particularly unique to the rare disease community. A lot of people will go to a doctor, and they might have a single disease and there obviously are mental health issues associated with that. But when you are looking at seeing, like you said, 12 specialists, that, to me, is crazy and adds hugely to the burden. Telemedicine I think is something important that maybe we can touch on later. Also, I do want to talk a little bit more later about how we can help doctors better understand rare diseases and maybe not be as scared of them.

Medical problems are stressful for everybody, but there are certain stresses that have a greater impact on patients with rare diseases. When patients and caregivers approach a doctor with these issues and with mental health issues, is there a stigma attached to this conversation? Are patients reluctant to talk about mental health issues related to their disease? And the other part of that is, are physicians reluctant to ask about it?

Amy Hunter:

We did not research this stigma question, and maybe the other panelists can comment. My feeling through exposure to the mainstream media is that there is a lot of willingness to have the conversation in a more public sense than we have had before, which is a good thing - a positive thing. People told us through our study,

in terms of interactions with rare disease healthcare professionals, is that there seems to be a huge reluctance on the part of health professionals just to ask the question, how are you doing? Or how are you coping? How are you feeling? It is unfortunate because for those simple conversations, you do not have to go into being a psychotherapist. Those simple conversations can be very powerful and can be very valuable because it is just about validating how people are feeling, and that came through there very strongly.

“There seems to be a huge reluctance on the part of health professionals just to ask the question, how are you doing? Or how are you coping? How are you feeling? It is unfortunate because for those simple conversations, you do not have to go into being a psychotherapist. Those simple conversations can be very powerful and can be very valuable.”

I am not sure whether the healthcare professionals who are not asking those questions just do not have time; it does not occur to them, or there is an unwillingness. I guess it varies between individuals. I could quite understand, certainly with the under-funding of the mental health services here in the UK, that healthcare professionals may be concerned about: ONE: opening that can of worms and whether they can handle that conversation effectively and sensitively themselves. TWO: They may feel that if there is a case for referring someone to receive professional psychological help, whether that is going to be available and whether it is going to be appropriate for that individual.

Kym Winter:

It is a very interesting question that is being raised: why are physical healthcare professionals not asking more? Just those simple questions as Amy says that are so validating to patients. Just that: how are you coping? How are things? How are you getting on? Not necessarily leading to do anything more than that. Often, it is the acknowledgement that, this is a lot to be coping with, to be bearing. That is

fundamentally therapeutic. And I think we forget that. It is not about needing to ask a question and then send someone on necessarily to a mental health professional. I think it is just the confidence of being able to ask the question; to bear the discomfort perhaps, of someone being angry or upset or disappointed or frustrated, without necessarily being able to provide an immediate solution. Just by saying, “Yes, I get it. This is hard.” That is enormously powerful. That would be incredibly powerful for the healthcare professionals to learn, and to be more confident in asking, Are you okay? How is it going? It is simple.

“Just by saying, “Yes, I get it. This is hard.” That is enormously powerful.”

Kathleen Bogart:

I love that point. “Are you okay? And how are you coping?” These are things healthcare providers can have in their back pockets to ask. On the American side, I did a large-scale study on quality of life and mental health among people with rare diseases (Bogart KR, Irvin VL. Health-related quality of life among adults with diverse rare disorders. *Orphanet J Rare Dis.* 2017 Dec 7;12(1):177. doi: 10.1186/s13023-017-0730-1. PMID: 29212508; PMCID: PMC5719717). We have had about 1200 participants with 200 plus different rare disorders. We found that the measures that we used were measures that already had norms in the US population and had norms for common chronic conditions. For every domain that we assessed in quality of life, people with rare diseases scored significantly poorer than the US population and people in the US with common but chronic conditions. This really does point to an extra challenge with people with rare disorders, and specifically, I want to point out that for depression and anxiety, people with rare disorders were more at risk for depression and anxiety compared to 70% of Americans.

“People with rare disorders were more at risk for depression and anxiety compared to 70% of Americans.”

We know that this is a very at-risk group. Just like what you all have been saying is happening in the UK, it is also happening in the US. I think doctors are strapped for time, and as you say, do not want to open a can of worms that might take more time and energy. Of course, they are well-meaning, but the way the pay schedule is set up, you have like just a few minutes with your patients. There is that hesitance. But also, rare disease patients, especially those with conditions that are not visible, are very acutely aware of being told that it is all in their head. They may be afraid to ask for mental health support. The doctor might even be aware of this, as well, and afraid to ask because it might be invalidating. But what I want to just point out here is that you can have a conversation that separates, “I think that the physical problems that you are presenting with and reporting are all due to a psychological problem.” There is a way to separate that from, “You are dealing with a lot right now. How are you coping? I would like to send you to someone if you are interested who might be able to help you with the general uncertainty and discomfort that you might be experiencing.” Right? And I think that just taking another moment to clarify, “I believe you. I validate this. And it is important for you to have extra support, if you want it.”

Kym Winter:

Should we make the idea of mental health support just ordinary as part of rare disease care? As Amy said, “How are you doing? How are you coping?” It should be asked frequently and not be either under-played or over-played. It is just seen as one of the ordinary challenges of living with the rare disease. Of course, it is going to be stressful. Of course, there is anxiety involved. How can we help you? What can we do to support you? It does not mean you are being defined as someone with a Mental Health Problem, capital MHP. Does that make sense?

“Your job is to ask [How are you doing? How are you coping?] and that innately is therapeutic.” I think that is what we need to tell healthcare providers. I think helping to demystify that to the physician, saying, “You are

not supposed to cure their depression with this question, but asking the question actually helps.” I think that is what we need to make it, so that you do not have to get the perfect doctor.”

Debra Regier:

I am going to hop in here as that physician who is scared to sometimes bring it up. I feel like I need to take that clip and show it to my trainees and say, “It is therapeutic even if all you can do is ask. You do not have to fix it. You do not have to cure it. That is not your job. Your job is to ask and that innately is therapeutic.” I think that is what we need to tell healthcare providers. “No one thinks you have to cure this. You are acknowledging that it is the reality and you are saying, “This is the reality and I am going to be in your reality with you.” It is the same way of saying, “You need to see your cardiologist because you have a valve issue,” or you have some other issue. It is the same thing. It is just, it is another specialist. I think helping to demystify that to the physician, saying, “You are not supposed to cure their depression with this question, but asking the question actually helps.” I think that is what we need to make it, so that you do not have to get the perfect doctor.

There is an education series I am doing, and the one thing we realized is we needed to add an hour into how not to be the perfect doctor and it is okay to do what you can do. No one expects you to cure the person with rare disease. That is not your job as their provider. Your job is to live life with them and to be with them on the journey. How do we help physicians be okay with not curing it? Which is a weird and hard place. And I think that is where that underlying, “Why do they not ask? Why do they not do it?” It is because they really want to cure it and it is not always curable. It is treatable, absolutely, but it is not always curable.

Amy Hunter:

I think probably keeping an emphasis on those conversations need to be quite simple. It is probably actually an important message. A lot of people who took our survey, unfortunately, of the less than 50% of people who had been asked by their

healthcare professionals, how they were feeling, when these conversations went on, quite a significant proportion said that they came out feeling worse after the conversation. Now, we did not dig into what happened in those conversations so I cannot really comment further, but I think that message about just keeping it simple and showing that you understand that there is an emotional burden and people may be struggling. They may be feeling stressed. That is helpful.

What you are saying about wanting to cure as a physician is interesting, as well, because of course, one of the things that I do not think we touched on earlier about rare conditions and why they can be particularly difficult to live with is that there are very, very few curative treatments for rare conditions. There are between 6,000 and 8,000 individual rare conditions, in Europe, there are only a few hundred licensed treatments. On top of that, because of the way our health system is set up, then there is often a struggle to actually get funding so that the medicines are accessible to individuals through their health services. It is a high-stakes situation for people with rare conditions. You have a diagnosis; you feel like you are getting somewhere and the physicians obviously want to cure their patients. But a lot of people feel then that they are up against a big wall in terms of what is actually available, and I think that is quite a major element in terms of having impact on people’s mental health.

Kym Winter:

This links us back to the diagnostic odyssey. There is a tremendous pressure on that healthcare professional to come up with the goods to be the best that they can be. Of course, that is a wonderful thing, but of course it is very inhibiting sometimes and it is a real pressure on that healthcare professional, too. I am quite interested how the impact of the diagnosis odyssey affects the healthcare professionals; that fear of getting it wrong, the desire to get it just right, to want to be the best is all in the mix, I think, with this.

Sean Sanders (host):

Thank you. That is the next part I wanted to talk about - the psychological impact of this diagnostic odyssey, which I think is something that is fairly unique to the rare disease community. And we all know how long it can take sometimes to get a diagnosis. First, why

would somebody necessarily want a diagnosis if no treatment is available? And together with that, what are the psychological impacts of not getting a diagnosis

Kathleen Bogart:

This question is a very real experience for many people. As Amy was saying, most rare diseases do not have a cure. Some have treatments, but it is quite likely that when someone gets a diagnosis, it is not going to be, “Okay, well, we are as the British would say, done and dusted and we will just apply that cure and figure it out.” But there is a lot of value to just having that name of the rare disorder. It really opens a lot of doors. It allows the person then to connect with professionals who have the most expertise in that area. Crucially, it allows them to connect to the rare patient organizations. For many rare disorders, there is at least one organization that is run by people who have the condition, who have family members with the condition, or who otherwise are passionate and expert at the condition.

Kathleen Bogart:

These groups: I spent a lot of time working with them. I am on the Scientific Advisory Board for one that supports people with my own condition, Moebius syndrome, and they can just be so valuable. Being connected with them really opens the door to a community and identity, so others can meet people with their own experiences for the first time, because rare diseases are so rare and geographically dispersed, you would never find someone just in your hometown, even at your local hospital. You really must go these extra steps to connect with a community that way. And now there is a lot of online ways to do it through Facebook and through other organizations. It really allows people to have a sense of what their life with the rare disease might be. It provides them with role models and with mentors, who have those conditions. The other thing I would just add is that we have some nice quantitative data to support the idea that having a diagnosis benefits mental health. In that same survey that I was talking about before, we found a significant correlation with length of time since receiving a diagnosis and lower anxiety and depression. So regardless of whether these people actually had treatments or cures, simply having a name and having kind of a road map eases this mental health burden.

“Having a name, a framework for people to start to think about what the disease is can really help.”

Kym Winter:

I think having that label can help reduce isolation. Kathleen talked about reaching out to people who have similar experiences, but also just in interactions with your existing community, with your family and your friends, who can find it hard to understand what you are going through, especially before you have the diagnosis. Having a name, a framework for people to start to think about what the disease is can really help. That can extend to non-medical services, as well. Certainly in the UK it can help families, for example, get the kind of support they need for their child in their education setting, for social care, for respite care for families and that kind of thing. Even though a lot of those things should supposedly be based on need, and nothing has changed from the day before you got a diagnosis to the day after, your needs and what kind of support you need in education or for social care may not have changed. What we find is that having that diagnosis, having that label can suddenly open doors and just make life that bit easier. Also, having diagnosis can bring knowledge in terms of likely progression of a condition, so prognostic information. And for serious conditions, of course, families it can be very important if you are looking to have more children and you want to have information to inform those kinds of decisions, as well, a diagnosis can be incredibly important for in all these different ways.

For me what is so important about having a name for your condition ...is that it gives you ...access to a community.... Just look around this room, and when you are having those really dark or difficult moments, you know that there are other people in this room out there in the world who will understand, who will be going through something similar, or will have gone through something similar.

For me what is so important about having a name for your condition or conditions, is that it gives you, as I think we are all saying, that access to a community. Often

when we are running workshops, what I need to do is just look around this room, and when you are having those really dark or difficult moments, you know that there are other people in this room out there in the world who will understand, who will be going through something similar, or will have gone through something similar. And the enormous, sort of powerful potential of that, to ease that sense of aloneness and isolation, which of course can lead on to depression, anxiety, or despair. I think despair is something that often captures for me something more of the rare disease experience for some people.

Sean Sanders (host):

I want to talk about some of the solutions to the issues that we have raised. I think you have brought up some fantastic issues, particularly around what physicians can do, asking, “How are you?” The simple questions. Trying not to be perfect, trying not to treat everything at the same time and do it perfectly. But do you have any other suggestions? I am thinking particularly in terms of helping physicians understand how to treat these patients holistically, and also on the education side, recognizing the unique challenges of rare diseases.

Debra Regier:

We teach rare disease doctors and primary care members of the team about rare disease and the unique aspects of the diagnostic odyssey. Whether or not you, the health care provider, think you are the expert or not of rare disease, because you helped them get to that point, you have become the expert and figuring out how to be in the unknown with them. Even if you talk to the world expert, they might say, “Oh, I have never seen that”; “I do not know what to do with that.” I am thinking back to a mom I saw last week. We were chatting and she said, “Hey, I do not know what to do about this.” I messaged out all the other experts in the field and, they were like, “We do not know”. I go to the mom’s Facebook group and find out if any other mom has seen this. Between my talking to the doctor, and talking to the Facebook group, we found one other person, I called up that doctor and said, “Hey, what did you do for this?” And they said, “Oh, we did this, but it did not work.” We do not know always what to do?

“The health care worker says: “We are going to jump in with both feet, and we are going to be on this journey together with you and your family and your child. We are going to listen and we are going to think and we are going to be creative together.”

You have to have willingness to listen and willingness to try things, and willingness to say, “We are going to jump in with both feet, and we are going to be on this journey together with you and your family and your child. We are going to listen and we are going to think and we are going to be creative together.” As I create educational modules for trainees, so about 10% of the genetics residents in the country come through my training program, and about 20% of those training in metabolic, it is a certain type of rare disease, come through our training program. We also run national and international training programs for researchers and primary care doctors who are interested in better understanding rare disease. As we do all of this and try to be very intentional about it, you do not have to be perfect, but you must chat with them. You must be creative with the family. You have to listen, and think, “Okay, who can I contact? What other resources can we come up with?” This idea of how we teach people need not be perfect, but must be creative, and that is a weird place, that is not what we have trained doctors to do. I can guarantee it is not in the US, and I doubt that it is not in the UK, either. Because physicians must be time efficient, they use standard protocols, they use best scenarios, and suddenly we put them into a milieu when there might not even be a protocol and you are going make it up as you are going. You want do no harm, and yet you do not know if what you are doing is harm or not, so you are going to go for it and you are going to try it. But I think by communicating to people, doing nothing is the harm. It is best to try something. Listen, talk, communicate. Doing your best is the doing no harm in that situation in rare disease sometimes. If there is a protocol, use it. There might not be one. Our institution is also looking at how do we create protocols for rare disease to try to help those primary care

physicians, so there is a place to start. So those are some of the things we are trying here at the rare disease institute to try to help support providers if they do not have access, or if families are long distances from someone who might know some of those things.

“Doing nothing is the harm. It is best to try something. Listen, talk, communicate.”

Kathleen Bogart:

I want to echo a lot of what Deb has said so beautifully. Implicit to what you are saying, Deb, is I am hearing that you are a great listener to your patients and the creativity that you talk about, it involves listening to patients and learning from them and reaching out in unconventional channels. You talked about the Facebook group. I think to be an excellent provider, supporting people with rare diseases, those are the skills that you need, because there is so little information, you really must be creative in kind of taking it from as many angles as possible. And often the patients and their communities really are the experts.

Debra Regier:

I cannot tell you how many patients have said, “I went to the emergency room and the doctor told me they knew more about it than I did” and I said, “Oh, did you laugh at them because you should have.” And then, yeah, I laughed out loud and told them to call you and then you tell them, no, they are the expert. I just always laugh that physicians are not used to that. We are used to knowing and we are used to being the ones that know more, and this is the case where we do not. The family probably knows more.

Kym Winter:

I always really liked the term, “diagnostic odyssey” because it so perfectly encapsulates something. And one of the things we often talk to our patients who come and see us about, is the idea of a rite of passage which, of course, is linked to the idea of odysseys. And one of the rites of passage is that sort of loss of innocence. And what we mean by that is having to

accept that the doctors and nurses that you grew up with the idea of when you were younger, that are all-knowing and all-powerful, you have to kind of put that down a bit when you are living with a rare disease because everyone is learning as they go along. But there is a sort of unique game that patients must do as part of that. Physicians also must learn to tolerate living in the face of uncertainty which is, of course, what rare disease patients and families are doing all the time. We are all practicing and we are all trying to support each other in learning how to manage uncertainty and the unknown, and it is not easy. We do it better together, I think.

“Physicians also must learn to tolerate living in the face of uncertainty which is, of course, what rare disease patients and families are doing all the time.”

Amy Hunter:

There are some considerations to support primary care physicians with, especially, when people do not have a diagnosis. There are certain patterns of behavior that you might recognize someone who keeps coming back. They might be talking about a different problem, each time they come back. It is important to recognize that there might be something going on. Okay, you have run a few tests for common conditions, they have come up clear. It is important we have got this phrase coined by an organization who works a lot, called Medics4RareDiseases and they coined the phrase, “To dare to think rare.” To start thinking, “Okay, I do not understand what is going on, but, I am not going to label my patient as neurotic. I am not going to dismiss their concerns. I am going to listen and I am going to dig into it a bit more.” And I think, obviously, no one is expecting every physician, especially every primary care physician to understand in-depth all the signs and symptoms for a huge range of rare conditions, but what we need to get to is a place where physicians do dare to think rare, they do not say, “Okay, I have reached the end of my road. I cannot go any further with this patient. That is it.” But then, maybe more they can do and it is important to think about those uncommon conditions, as well.

“Dare to think rare.” Obviously, no one is expecting every physician, especially every primary care physician to understand in-depth all the signs and symptoms for a huge range of rare conditions, but what we need to get to is a place where physicians do dare to think rare.

Kym Winter:

This true in mental healthcare, too, where sometimes it is those who get referred to psychological services are those that are difficult patients or hard to help patients. In the mental healthcare field we need to get a bit more astute again about thinking, “Dare to think rare.” I certainly know patients who come with chronic anxiety through the mental healthcare system. And then they had been found to have a rare condition, a physical thing that has affected their adrenaline systems, and that is what has been causing the chronic anxiety. So as mental healthcare professionals we need to be thinking rare, too, not just working with the symptoms.

Kathleen Bogart:

I wanted to raise another issue about how doctors can support their patients; why they might be reticent to refer out to mental healthcare? I want to remind the audience that it does not always have to be referring out to a service that requires payment. There is such a strong benefit to connecting with these rare disease organizations that we mentioned earlier. I would recommend that any doctor, especially the doctor who provides the formal diagnosis or even a tentative diagnosis, to let the patient know about rare disease organizations that exist. In America, for example, we have the National Organization for Rare Disorders, and they have a list on their website of all the organizations, member organizations that support a different rare disorder. It could be easy for a healthcare provider to just pull up that list and suggest a relevant organization.

Kathleen Bogart:

I wanted to talk a bit more about the stigma that people with rare disorders experience, and how these organizations can benefit them. As I mentioned earlier, those with rare and invisible conditions are often not believed. Right? But also, those with visible rare conditions are noticed but kind of unrecognizable. I say that about my own condition which involves a facial paralysis. There is very little public awareness about Moebius syndrome or facial paralysis in general, which often kind of falls under the rare disease umbrella. With visible conditions, strangers will often notice the person's unusual appearance immediately. They may not know how to explain it because they have never heard of it. This can be very distracting for others. Others may misunderstand the visible symptoms to mean something that they do not mean. So maybe, if the person also has intellectual disability, where that might not be the case.

These sorts of challenges, stigma occurs for both types of conditions, right? Both of those buckets. And can really be ameliorated by connecting with communities like them. I like to talk about attending the Moebius Syndrome Foundation conferences, which occur usually in person every couple of years. You hear that it is life-changing for people to suddenly be in a room full of people who look just like them and feel no need to explain. Suddenly, they are the majority group. They look like everyone else and you hear the same thing for people with invisible conditions. Suddenly, they are around people who simply understand their conditions and believe them. Connecting people to these sorts of groups indeed actually has measurable benefit. We have studied people who attend versus those who do not attend those Moebius conferences, for example, and have found increased social support and reduced stigma when they do attend these conferences. Again, I really encourage healthcare providers to help people get involved in some sort of community.

Amy Hunter:

I would like to echo that exactly, Kathleen. We found that with our UK community, in the work that we did a few years ago that came out as such a strong message, and I wish I had known about this organization. I was left without knowing where to go after my diagnosis. And very, very few people are signposted by their healthcare

professionals, unfortunately, even once they have a diagnosis. Of course, because there are so many individual rare conditions, there is not always a patient organization or even a Facebook group with your condition, especially for ultra-rare conditions. Sometimes it is just inevitable that you are going to have to look internationally to find more of a remote community, and I would just like to put a shoutout that a very useful website called RareConnect exists (rareconnect.org/en), that physicians can signpost to, which is for individuals who are struggling in that way to find an existing group. RareConnect will help people with a diagnosis to find individuals elsewhere in the world, even if there is not a structured, a formal patient organization already. I think that is helpful.

Kym Winter:

I want to talk about the importance of keeping awareness alive for patients; that there are these patient communities. It can be quite frightening for somebody to take a step into being with others who have a condition. You are frightened what you might find out, you are frightened what you might hear. Some people are more natural joiners of things than others, so that idea of sort of just keeping it gently available, "There is this organization, have you thought of contacting them?" Because usually we find, nine times out of ten once people do make a connection. If they can just connect with one or two people even, it is incredibly powerful and supportive. But it is sometimes about timing when someone is ready to take that step.

Debra Regier:

I agree completely about the timing, so especially in conditions where we might have a shortened lifespan, that is really hard for families to hear from other families that have lost a child, especially. I warn them before they go on, there might be others who have lost a child, if you are not there yet, do not go onto that Facebook group yet. Do you want to talk to a family? Then I try to do one-on-one connections to a single family, if I can, if they are not ready for that. But again, saying, "It is there when you are ready." But it must be at the right timing, I agree. It is a huge resource, but the timing is essential.

Sean Sanders (host):

There is one thing I want to just touch on very briefly. I know that not all rare diseases have a genetic component, but I think something like 70% do. If you could just briefly talk about what genetic counselors do and how it differs from what psychologists might help with.

Kym Winter:

I was thinking about it earlier was awareness from our perspective that the emphasis in genetic counseling is really sort of information giving, about understanding the implications of the condition over time and for having further children or wishes like that. But it is not often more than one or two sessions. I do not think there is a good general understanding about the difference between genetic counseling, which is very focused in a particular way, and psychological counseling, which is unpacking the meaning of that diagnosis for you personally and for your family over time. So often patients come to us, they are a bit surprised and they might say, "Oh, I thought I had counseling. Oh, I can have more of them?" Well, this is quite different. I think there is not a good understanding still of the difference between genetic and psychological counseling, and maybe we need to work a bit more together on that over time in the rare disease community, too.

Debra Regier:

I agree. I wish we had a continuum. If I had the perfect role, the perfect clinic... We can do that later, the four of us can get together and create the perfect role. We would have a genetic counselor and a geneticist that starts the progress with them. The genetic counselor gives that information, does like that first line kind of gives the bad news. What they are good at is giving the bad news and making sure that that family can survive that hit of the diagnosis. Here we have been talking a lot about how positive that experience is, getting a diagnosis. But there are families that do not want a diagnosis because, in their soul, they do not feel like it is going to be the diagnosis that they want, so they do not want a diagnosis.

There is always that conundrum we have of when a person does not want a diagnosis. But when there is a diagnosis, if it is not one that they wanted, one that might not have a treatment at all, or for sure not

a cure, or have shortened lifespan, that initial, “How do we help you cope with today? How do we help you cope with the next few weeks of your life?” That is what genetic counselors are really trained in, that is what they are good at. That does not look at, “How do I now keep living my life for the next months, years, decades?” That is when I need long-term support. I need that long-term therapist in their community, hopefully. Someone close to home, someone who they have a longer-term relationship with.

In all honesty, it needs to be someone who does not give the bad news. I get fired on a regular basis by families because I am the one who gave the bad news. And I give them that right to fire me, because they need someone to hate in that minute. And that is okay, that is fair. And I think genetic counselors are good at being fired in that situation because it is just so hard. But I want a therapist, a psychological therapist to kind of be there, that did not give the bad news, that kind of gets to rescue them and gives them a chance to feel like, “I am not alone in this bad news.” So yes, geneticists and genetic counsellors, I think we try to get them through that first, I always say days, weeks, maybe even a month or two, but then they need someone closer to home, they need someone in the community, and thankfully with Zoom that community has broadened, with Zoom or telemedicine options. That is one thing we have learned. Pandemics have taught us well how to create broader, bigger communities. It is important that we almost do a transfer of care. That would be my perfect rolled word, almost be a transfer of care.

Kathleen Bogart:

To mention timing: Sometimes you are not okay with getting a diagnosis at that point. Sometimes you are not okay with jumping headfirst into that big community. And I think that really is the value of the clinicians that are here today, of helping people navigate that timing. And it can be done but it is a very individual thing. This is all wrapped up around identity, so working with that person to come to terms with a changed or additional aspect to their identity can take time, and I think we have done a pretty good job of talking about a lot of different options and resources that are available to people when they are ready for them.

Sean Sanders (host):

Great, well, thank you, Kathleen, and thanks to everybody. Thank you once again to our fantastic panel and to Fondation Ipsen for enabling this conversation through their kind sponsorship. Good-bye, everyone. Thank you.

Journal Club

Article of the month

Medical students' knowledge and opinions about rare diseases: A case study from Poland

Domaradzki J, Walkowiak D. Medical students' knowledge and opinions about rare diseases: A case study from Poland. *Intractable Rare Dis Res.* 2019 Nov;8(4):252-259. doi: 10.5582/irdr.2019.01099. PMID: 31890452; PMCID: PMC6929592. https://www.jstage.jst.go.jp/article/irdr/8/4/8_2019.01099/_article

This issue of the Gazette discusses training of health care workers regarding rare diseases. Very little research has been conducted in this area. In this article from Poland 346 medical students were questioned.

The study showed that nearly all medical students (99%) perceived their knowledge about rare disease to be insufficient or very poor. The future doctors did not feel prepared for caring for rare disease patients. The authors concluded, “most future physicians do not possess knowledge about rare diseases, there is an urgent need to raise the awareness on rare diseases among medical students and educate them about such diseases.”

This message also comes through loud and clear from the Gazette experts. It is important for patients and their families to know this as especially for individual rare diseases the patient and their family may know more than their doctor.

History Corner

A Brief History of Mental Illness: From Ancient Times to Medieval Islamic Medicine.

by Florian Delval

Mental illness has always intrigued and fascinated humanity. Since ancient times, attempts have been made to understand and treat it - sometimes with surprising accuracy. Archaeo-anthropologists discovered that trepanning was used as early as the Neolithic (10,000–4,500 BC), likely as an attempt to cure evil spirits. The first written traces of mental illness appeared during the ancient period. One notable example is the *Ebers Papyrus*, one of the oldest papyri on medicine. This papyrus, discovered in Luxor in 1862 by Edwin Smith, and purchased by the German Egyptologist Georg Moritz Ebers a few years later, mentions several mental disorders as signs of hysteria or strong emotional distress. At the time, there was no effective treatment, but medical practitioners began to form theories about what might cause mental illness. Thus, many references to divine punishment or presence of evil spirits were made over the centuries.

The notion of balance between mind and body was also present in many societies around the world. According to Prof. Dinesh Bhugra, insanity was, in ancient India, a combination of “metaphysical entities, supernatural powers, witchcraft or evil powers”. However, as early as 6th century BC, it was considered that insanity and mental health disorders could also come from a disturbance in the balance of various elements that make up the human body. This was stipulated by the *Charaka Samhita*, an integral part of Hindu *Ayurveda* - the knowledge of life. The various elements that make up the human body can also be found in the ancient Greek Theory of Humors, of which Hippocrates was the greatest exponent. Hippocrates and his Kos School of Medicine distinguished themselves from their contemporaries by rejecting beliefs of that era, which attributed to *mania* (mental illness) a form of divine warning or punishment, as shown in the Greek mythology. The story of Heracles is an excellent example. Victim of goddess Hera's jealousy, Heracles was struck with madness after ingesting a potion - killing his wife and children in the process. For Hippocrates, the reality was quite different, and he stated in *De Morbo Sacro*: “It

seems to me to have nothing more divine or sacred than the others [...]. They have covered their insufficiency with the mantle of divinity [...]. The brain is at the origin of this affection as of all the other very great diseases”.

For Hippocrates and his Kos School of Medicine, *mania* was a matter of medical practice and therefore originated in an excess of one of the four Humors: black bile. Marianne Massin explained in her 2015 article entitled *Creative Mania, Ambivalences and Twists* that: “It is the preponderance of the black bile that generates the melancholic mood, which is also characterized by instability. When heated, the black bile tends to expand and pushes one to go outside of oneself, which facilitates a propensity to imitate, imaginative power and all sorts of forms of ectasis or crazy behavior, *manikos*.” For Hippocrates, mental illness was a disease that originated in the brain. Within his writings *On the Sacred Disease*, he specified that “it is through the brain that we think, and it is through it, when it is not healthy, that we are mad, that we are delirious, that terrors beset us”.

Romans were also strongly influenced by Greek mythology, and their medicine relied heavily on Hippocratic's theories. Great thinkers such as Cicero, statesman of the Republic of Rome in the 1st century BC, made their own statements on mental illness. A figure of stoicism, Cicero believed, among other things, that passion had different degrees and that, at a certain stage, it caused madness. Perhaps passion as a symptom of the soul's illness? Cicero stated in his *Tusculanae Disputationes*: “between emotion, passion, vice and madness, there is no difference in nature but in degree. So much so that we can say that we are responsible for our madness, at least at birth. Madness is only the absence, at the origin, of self-supervision”. A few centuries later, Galen would dust off and modernize Hippocrates' theories. Galen distinguished himself by using a “single symptom” approach, enabling him to differentiate certain mental disorders (such as chronic melancholia, excitement, or madness). He was also renowned due to his meticulous examination of individuals' behavior.

Medieval medicine was strongly influenced by that of Antiquity. During the ear-

ly centuries of Islamic empires and states, methodical care of patients was implemented. For the first time, facilities were dedicated to them. An asylum for mentally ill patients was built in Fez, Morocco, as early as the 8th century. Other similar institutions followed suit, opening in Baghdad in 705 AD, Cairo in 800 AD and Damascus and Aleppo in the 13th century. Heavily influenced by Greek medicine, Islamic medicine was remarkable in that its advancement was far ahead of its time. A more modern vision of mental illness was brought forth with translations of medical and philosophical treatises from the Greek world carried out by scholars. While Ancient Greeks had a more bodily approach to mental illness, Islamic medicine took on the task of modernizing the way in which mental illness was perceived, understood, and treated. It was the first to clearly distinguish diseases of the body and of the mind from each other. This decisive difference marked the early days of the psychosomatic approach. In the tenth century, Ishaq Ibn Omrane, author of the Treatise *On Melancholy*, pushed the hypothesis that “the soul follows the body, but the reverse is also true”.

Rhazes, a Persian physician working at Baghdad, introduced the term “psychotherapy” and laid the fundamental foundations for the treatment of the troubled mind. In charge of the city's Hospital, he was one of the pioneers in the treatment of the mentally ill, dedicating an entire wing to them within the facility. Avicenna, two centuries later, in his *Canon*, put forward the idea that mental illnesses should be treated by psychic remedies, combined with the use of drugs/pharmacopoeia. Psychological support for patients thus spread throughout the medieval Islamic world. In the article entitled *Islamic Medicine, 1000 years ahead of its time*, Ibrahim B. Syed states that “the Arabs brought a refreshing spirit of dispassionate clarity into psychiatry. They were free from the demonological theories which swept over the Christian world and were therefore able to make clear clinical observations on the mentally ill”. Ahead of its time, Islamic medicine was already using music therapy, comic performers, and occupational therapy during the Middle Ages, thus showing its capacity for analysis and a real innovative spirit to treat those who were, and still are, vastly misunderstood.

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What's up?

Highlights of the month

Movies to move you by Morgan Packer

Mental illness in cinema is one of the essential themes on humanity, interpreted and depicted from the classics to modern day films. While there are certainly more films than we can count that cover this topic, with notable shoutouts to Silver Linings Playbook (2012), Donnie Darko (2001), Good Will Hunting (1997), and of course, One Flew Over the Cuckoo's Nest (1975) here are some of my personal favorites:

1. Based on a true story, **Brain on Fire** (2016) portrays the rapid decline of 21-year-old Susannah Cahalan (played by Chloë Grace Moretz), whose perfect life is suddenly uprooted by strange behavior, seizures, outbursts, and severe mood swings. Her diagnostic odyssey passes through several stages, with doctors initially believing that she may have bipolar disorder, then schizophrenia, until a specialist manages to identify the main cause of her symptoms – a rare disease called anti-NMDA receptor encephalitis. While many professional critics have poorly rated this film, fans are grateful for its honest depiction of struggling with an undiagnosed rare disease and its consequential psychosocial impact.
2. **A Beautiful Mind** (2001) is based on the true-life story of the renowned American mathematician John Nash, played by Russell Crowe. This film tells the story of a brilliant man affected by paranoid schizophrenia, his hallucinatory relationships, how his illness affects his wife and loved ones, and despite all odds, winning the 1994 Nobel Memorial Prize in Economic Sciences for his research on game theory.
3. **Garden State** (2004) directed, written and starring Zach Braff, depicts the long-term effects of a heavily medicated childhood with bouts of depression. He meets Sam, afflicted with epilepsy, and also happens to be a pathological liar. Despite their two separate and challenging circumstances, they fall deeply for each other through unconventional interactions in the State of New Jersey. Huge film bonus: Garden state has an absolutely fabulous Grammy-Award winning sound track still worth listening to in 2021.

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