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Proem

For twenty-five years, physicians diagnosed my periodic episodes of fainting, falling, disorientation as cardiac. Eventually, in my 50s, I learned I had multiple Sclerosis, not cardiac disease – repeated misdiagnosis. Multiple Sclerosis is not a rare disease. I come only this close to appreciating the trials and tribulations of experiencing an undiagnosed illness. Something is wrong, I know it, I feel it, why can't you name it and treat it? February 28th is Rare Disease Day. Twenty to thirty million people have rare diseases and struggle to name their constellation of conditions and find treatment. I reached out to my colleague, Doug Lindsay, who I met through PCORI (Patient-Centered Outcomes Research Institute)'s Rare Disease Advisory Panel. Let's jump right into our conversation.

The fragility of health for Doug Lindsay 01:57

Health Hats: Doug, thank you so much for joining us. I'm excited that you're here. I don't think I only met you not that long ago. And we were on a call together. I believe the PCORI Rare Disease Advisory Panel. You pushed all sorts of buttons for me. Good buttons. And I reached out and hence this call. I

wanted to start introducing yourself to talk about what was going on in your life when you realized that health was fragile.

Doug Lindsay: Yeah. I learned that from my mom. From about 18 months on, it was very challenging for her to pick me up. She did pick me up when I was five and choked on a jawbreaker and saved my life. But that was generally the level of the situation, it would have to be for her to risk doing something like that. My mom just had a lot of health problems. And we had no answers, and she was a make-do person. She didn't see herself as sick as she was, even as the years progressed. Fourth grade was the last year she could go to a parent-teacher conference because, in the fifth grade, I was on the second floor of the school. That's not usually what you expect of a woman of 38 is to be able to have to forgo meeting with teachers if there are 12 stairs. My mom was just very sick for my whole life increasingly. And then also my aunt as well. Every day, I would play basketball or something during the summers, but I would swing by my aunt's to tie her shoes because she needed the shoes tied well and tightly. But she couldn't even tie them herself. It seemed very much like part of life, but it was in the sense that it could be something that was just part of the tapestry of your day, but it was also something that was part of life. It wasn't like everything was going fine, and then there was one day you realized the fragility.

Personal medical consultant finding answers 04:10

Health Hats: Let's do a more traditional introduction. And tell me a bit about what you do professionally and something you do for fun.

Doug Lindsay: So much of my life is wrapped up in the health sagas and odysseys that I've been a part of that those answers make sense more when you understand my story. But right now, I am a personal medical consultant. I am somebody folks with some means can hire. And I join their family for a year and see if we can get someone with a rare or complex condition unstuck. If they're stuck in the medical system, we try, I try and figure out how and work with them to get them unstuck. Get them a diagnosis or a care team working or get them treatment. That's a challenge because when you're neither the patient nor the doctor, you're almost like the zookeeper that brings the pandas together and goes, oh boy, I hope something good happens. After all, you don't have an intrinsic authority anymore. Either the moral authority of that of the patient or the authority of the physician. So that's what I do professionally. I like to drive. I like hitting a back road and that kind of thing. And I've been looking at getting back into fly fishing, which was one of the things I loved before I got sick at 21. I worked in a fly shop and spent my high school years in a fly-fishing club with folks who were decades and decades older than me.

Rare disease as an equity challenge 05:31

Health Hats: The thing that inspired me was in the conversation in the rare disease advisory panel at PCORI, you were talking about rare disease as a disparity as an equity challenge. Could you talk more about that?

Doug Lindsay: PCORI is the Patient-Centered Outcomes Research Institute. They had a congressionally mandated list of things they needed to do when they were set up. One was a Rare Disease Advisory Panel. And if there's going to be a panel, then somebody's got to be in charge of it. So, it's another fellow named Matt and me. We have about 15 or 20 panelists from every walk of life from industry and things. I represent patients, and some others do as well. We were in this meeting, and we were talking about the future of PCORI, an amazing organization set up ten years ago to put motive, to put money, and push behind an agenda aimed at getting information that helps patients decide what to do at the bedside, patients, and doctors. It is a great mission but fitting rare diseases has been challenging. It may be far easier to run a study with 5,000 or 15,000 heart patients comparing one treatment to another than to find a rare disease study because 19 out of 20 rare conditions don't have a recognized treatment. If most of your research is comparative effectiveness research, comparing treatment A to treatment B, and you have a population with no identified treatment, you've got a bind. But that bind extends so much further. Even though I lived the rare disease life because of my family, I was unaware that 25 to 30 million Americans suffer from a rare disease. Then it was easy to find that the average time to diagnosis is seven years. For me, if you don't count me diagnosing it, it would be six years. But for my mom in 1984, on a page in her records, all the information was there, and it took another 22 years for her to get a diagnosis. That's a long time. I started to look at the stats on rare diseases. Because of the roles that I occupy in these organizations and because of the continuing conversations we're having about health disparities and social determinants of health and such, it just seemed to me that this was the time for this conversation. And that is that there is a group called rare disease suffers. We don't necessarily even see ourselves as a group because the premise is that you are the small group, the tiny population with this rare problem. But when united and it's a large population. When you look at the health outcomes of that population, they're awful. Seven years to get diagnosed. 95% have no approved treatment. The stats go on and on from there. With the current rate of new treatments, it would take another 2000 years for each of these 7,000 identified rare diseases to get treatment. But some don't, aren’t identified. So, when I saw this, I thought this was essential at a place like PCORI, at a place that puts patient outcomes at the center of what we focus on, rare disease needs to be considered an equity group because there are initiatives all over the world and all over this country aimed at remedying health disparities. And if rare disease isn't seen as one, all those efforts won't even be trying to help us.

Commonalities of people with rare diseases 09:46

Health Hats: So the thing that's interesting to me about and thinking about this and thinking about as a PCORI board member implementing, is that if the focus is on treatments for an individual diagnosis, So meaning that, there's, I'm making this up, but there are a thousand people in the country with this diagnosis, as opposed to thinking about this cohort of people that have rare diseases that are difficult to diagnose. And so that it's the, as you were saying that it is a large group and one of the common things is the difficulty to diagnose and think about what kind of research can be done to, I, I. I picture an algorithm systematically okay. We don't know what this is. Here are steps to narrow, whether it's narrow that it's neurologic or cardiac. Is that an appropriate way to go, or is there a different way to structure an algorithm so that you could cut the time in half from seven years to three years, three and a half years?

Helicopters, zebras, interns' disease in physician training 11:13

Doug Lindsay: I can cut the time in half right now. And I'll explain how. When doctors train in medical school, interns read about everything, where every disease you're reading about you have now. Because if you have a bellyache and you've been reading about all the things that can go wrong, you said, when did you become aware health is fragile. That's when doctors are becoming aware of how fragile this thing that's working could fail in innumerable ways. We are like a helicopter. Our body is conspiring to fall apart at all moments like that's how they see it suddenly. So, doctors suddenly get taken to the woodshed and told, no, he doesn't have this thing on the back page. You learned about the back textbook when you hear hoofbeats. Think horses, not zebras, right? Common problems show up commonly; rare problems show up rarely. Still, in the heuristic of busyness, common problems show up commonly that part gets remembered, rare problems show up rarely that part gets thrown aside such that rare means never. If I wanted to cut the diagnostic time for rare disease patients and their odyssey, I would simply remind people that there are zebras. They didn't say that don't think unicorns, don't think, Esquilax or some strange creature we've never heard of. I took that from the Simpsons, by the way. But you would try and understand that once doctors need an alarm bell, when a patient has been seen by a suite of folks, and no one has an answer, you need to say, maybe it's a zebra and not a horse or not just a horse since that's gone mad. So that's why this sort of health equity issue becomes important in these social determinants of health. In this pathway to solving things, just open the medical establishment's minds to reestablish that after the smart neurologist and the second smart neurologist have struck out, send the alarm bells up and go. Maybe this one's a Zebra. Because I always had to start with these crazy situations where doctors would concede I had the rarest condition in the world and then assume everything else was normal. So, I always started at this broad pyramid of, oh, that's rare that doesn't happen very often. And you're like, I'm already a zebra, why should you be surprised that I have rare aspects to my rare condition. So that's where this starts, even beyond a complex algorithm and stuff. Just throwing up a flag that says this one might be a rare disease patient that we are, and that's why we're struggling. We can adjust to that because I don't think that ever gets done. You end up with the doctor after the fact seeing, blah, blah, blah, hydrogenation, blah, blah, blah, some long genetic name, but there you need somebody to throw up a flag that says this might be a rare disease patient, and that's why we're struggling to fit it into common boxes. And that would shorten people's travel by length by years.

Undiagnosed disease programs 14:24

Health Hats: Yes. Are there clinics specializing in, we don't have a diagnosis yet, and we're good at looking at rare?

Doug Lindsay: Yeah. So, the NIH has an undiagnosed disease program, and it's new. When I was undiagnosed and sitting at home, there wasn't one, but they get a diagnosis 30% of the time. And while somebody, and that's like baseball if you hit .300, you're a star. That is that's what success looks like today. That's, those people are. You are taking challenging cases. Yeah, they're handling challenging cases and succeeding, and anyone who's been wandering in the desert with no diagnosis for years would gladly take a 30% chance at finding one. And that's where you start to see what a health disparity

looks like, as you say. If your foot hurts and you said you're going to go to the doctor, and there's a 70% chance they tell you, we don't know for the next two years, you would not find that acceptable.

Categories of differences across rare diseases 15:28

Health Hats: Okay. We've been thinking about some of the commonalities cross rare diseases. Yes. And then, there are the differences across rare diseases. Are there categories of differences that are not necessarily this chromosome or that chromosome? Can you help me out a little bit?

Doug Lindsay: You might find that there's a basket of neuroinflammatory conditions that are hard to tell apart. And you might find that there are degenerative conditions or rare cancers. Or so there are buckets within rare diseases. And one of the keys to moving forward would be to find opportunities to pool patient groups. The challenge is that comparative effectiveness research does not mean treatment A tried on populations, B and C to see which one responds better. It's two treatments, one population. And so even though we're comparing the effectiveness, it's not, like it technically. There's a need to look for studies that bundle some of these rare conditions together to help differentiate or establish sameness because at least letting someone know what area of medicine they're that their care should come from, or their diagnostic journey should primarily involve like that's progress. My mom had been sick 30 years, and you couldn't say for certain what branch of medicine was supposed to be the one figuring out what was wrong with her. If you have something with that level of clarity and level of murkiness and doctors as busy as they are, there is a chance for no one to take ownership.

Comparative effectiveness methodologies 17:31

Health Hats: It's interesting this comparative effectiveness business. I see elsewhere that comparative effectiveness says that a is more likely than B in this setting and these stances to be more effective, and they both need some evidence behind them to compare. Yeah. And if we're getting into areas that aren't traditionally the comparative research or that any research has been done on. So even if this is incarcerated people or people without homes. Goodness, pregnant women of color, which is certainly not a rare thing. There's much less evidence, so there's less to compare seems like a methodology challenge in our comparative effectiveness research work. How do you deal with that? And how does that come up in the rare disease advisory panel? I've attended two.

Doug Lindsay: I'll tell you where it came up. I was working. I got to advise active one of the active trials. So, these were the accelerating COVID, like vaccines and therapeutics and stuff. So, this was the NIH umbrella for COVID research, and there were six or so active studies, and I was advising the one on immunomodulators, and then I ended up on, okay. We were looking at a study designed to see which medicines could prevent an immune system overreaction in hospitalized COVID patients. the coverups worse than the crime kind of thing, or you over-correct into the skids. Sometimes people beat the virus, but they turn up their bodies so much that their immune system takes them down to long COVID. And that gets to the poor outcomes. So long, COVID is just a bubbling, bubbling pot on the stove that never seemed to settle down. This is where you can die. From the immune overreaction. But people talk about a sufficiently powered study. So, what that means is this sort of in layman's terms, coming from a

layperson who has never gotten to run a study, is there's a premise that there's a size required to create a quality of data. You know that ten people are anecdotal, and 10,000 people is a study. And yet what we ran into sometimes is that in my condition, when we were looking at surgery, I was able to track down 32 cases worldwide. Ever. That was still the best evidence we had and had to draw from. So, part of what happens is that best practices in other parts of medicine require studies to be large enough, well-populated enough, and standardized enough that you get defensible solid statistical conclusions. But if you're dealing with a population, that's a statistical anomaly. You may have to revisit that idea. Because if we wait to find 5,000 of something of which there's only a hundred of, we have certainly not helped.

Using existing models in new fields. Learning from tiny populations 20:59

Doug Lindsay: But here's the thing about knowledge, right? When DARPA thought of the internet, they certainly didn't think of Tik Tok, and cat memes and expertise added to the collective canon of what we understand has other benefits, other ripples because what you do is you borrow models, you learn from things. So, when bioinformatics, this field of studying biology was forming. They brought people in from electrical engineering and cell biology, and they were all using the models from their field to see if they applied to this new area. Even if you do rare disease studies, one, you may have learned how to study other small populations in a successful way or in a way that failed, which can also teach, but two, you, you learn things. There's a disease called Castleman's disease, and it's not widespread. And our friend David Fajgenbaum, the physician at UPenn who found his own cure and wrote the book Chasing My Cure. Guess what? One, he repurposed a drug, and two, his condition involves an immune overreaction that can kill you. David Fajgenbaum's work has been very helpful in the COVID world. Because it involved that same kind of immune overreaction that study, I was helping to advise was looking into. So that even though studying that rare disease, and for example, SARS and MERS, those populations were small enough that you could call that a rare disease. They didn't spread, and they could have spread, but the 10 or 15 years we spent studying it helped us fight the pandemic today. So, these small populations that lead to answers, those answers don't have to die there. They spark things elsewhere

Health Hats: In a way, you're also saying about the method.

Doug Lindsay: Yes. The process of figuring out how to study a tiny population applies to another tiny population and learning how to work with small numbers in data in a reliable way is just as valuable as, Optum crunching, people, data sets the size of Portugal.

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Leave us with something 23:59

Health Hats: Yeah. So, if you wanted to leave us, the listeners and readers, with a couple of key points that are important for them to understand or advocate for those.

Doug Lindsay: Let me pull back one second. We want to calibrate; cause I'm just talking about Optum. Your listeners are folks who are already in healthcare, right?

Health Hats: Yes, I would say that I'm Health Hats because I'm a patient, a caregiver, a clinician, a quality management person, an informaticist, a boss. My constituency reflects that variety, but what kind of I think are they care about best health. And how do you learn to get to best health whatever hat you're wearing?

Rare doesn't mean never. Questions mean an opening 25:21

Doug Lindsay: If we want them to layout a couple of things, couple takeaways, the first is that rare doesn't mean never.

Health Hats: That's a good one. That's right. I like that.

Doug Lindsay: Next one, which is important across all of science and medicine: a question is not the same as shooting something down. If I say, let's run a study that does X, Y, and Z, and you say, how would that work? Sometimes people can leave with a tear in their eye and go, boy, he shot me down. No, it is it. Questions should be a conversation. And so if you're using questions to dismiss or shut down conversations, then you need to change how you're asking them so that people understand it's an invitation, or you need to change how you're using them. Because people go, oh how would that work? One way I've gotten success over the years is always taking questions as if they were earnest. When somebody goes, how with that work, they may get a phone call in nine months in which I explained in detail how that might work. But that's important too. So as decision-makers, as leaders use questions as a true invitation to hear from a community or from people or about new ideas, not as a way to shut down conversations. Okay. Because remember, people don't always have the best answer on the spot. So, if your boss asks you a question, you don't have an answer for anything, and he or she doesn't do it in a supportive way, you can say them. And I'm not bringing that up again. So that's how we're going to change our tone of voice to invite conversations. When questions remain, and questions remain in all aspects of rare disease. So that's how that fits in.

Rare disease as a health equity group 27:04

Doug Lindsay: I would say. That what's special about my suggestion of making rare disease a health disparity group is that health equity is a relatively new take on a topic of equity. And so this would be a population rising from the health equity from the health sphere, instead of being brought from society into the health sphere, like race or gender or something elsewhere, or class, or where you're bringing a well-recognized concern and applying it to healthcare, this would be going from health care up. But

because of this population, our patients, it's essential that happened. Because the challenges that a healthy person in another equity group faces can suffer in that equity group. You can solve a problem for one without budging the other an inch. So those are the first thoughts that come to mind.

More than 25-30 million people have a rare disease 28:11

Doug Lindsay: And the other is just to remember 25 to 30 million Americans have a rare disease. That's big. That's more than the state of New York, and so when you're thinking about what to do for the rare disease community, you're not taking a diversion to make a one-off concession for some person who's landed on your doorstep. You are making efforts to help a problem that reaches 10% of the population.

Health Hats: Wow. So, is you want to leave us with anything?

Rare Disease Day 28:48

Doug Lindsay: Rare Disease Day is coming up. That's February 28th. I'm working on an opinion piece that explains a bit of the rare disease population to the nation and makes this case for a health disparity group. And what's important is this doesn't take away from anybody else. This adds rare disease to the disparities that big organizations are already working on. And I think the people working to solve and remedy health disparities would be the kind of people deeply motivated at bending the branch to have a system work better for somebody who has a rare disease. So, I think this will be pushing on an open door, but the task is figuring out how to get somebody to pay attention to this opinion piece. If I had to become the chairman of this or the co-chair of this org of this board to soak in the stats truly, there are plenty of health-literate people, but there are plenty of just savvy folks for whom this is all-new, and they'd have to pay attention to my piece to decide whether it's worth placing. So that's what I'm looking for is I've got a piece to place for rare disease day at the end of February. If anybody out there wants to help, think of getting some opinion page editor to give it the time of day. And I don't say that as an insult like it's just that journalists are bombarded by people hoping to share a message. My message comes from 25 million people that nobody's ever heard of and that don't recognize they're a community. So, I think there's a real benefit in putting at least a tiny megaphone for one day on this article and then letting the rare disease community share it amongst themselves.

NORD National Organization for Rare Diseases 30:45

Health Hats: I will try to put this around the 28th. That wouldn't have been my usual queue because I have a few other pieces, but it seems like it would be fitting to publish this right around then. So, I will, and if you I have the article. Didn't you just recently have something published?

Doug Lindsay: So, I submitted it as a comment for PCORI's research agenda. I would need to rework it a little bit to add, make the focus rare disease day, and then explain all that follows. I can do that quickly. Yeah. I did want to add one more thing. So, when my mom was sick, all those years. Before getting sick, she was a math and chemistry, a double major who worked at Wash U med school in the biochemistry department. And the best she could do would be to have us rip out tiny articles from the newspaper, Dr. Donahue's column, things like that because she was starved for information. She was homebound, and

it was pre-internet. Yeah. And one of the things she ripped out that sat on a copper-tin on our hutch for years and years was Nord, the national organization of rare disease. And it rare disorders. So, nor if you are struggling to figure out what's going on with your health, or if you have a rare disease, a great place to start is NORD National Organization of Rare Diseases and a great place to support. For decades, these people have been trying to facilitate communication within the rare disease community. And I'm happy to work with and for PCORI, but I am also very happy to spotlight Nord. They gave me our first clues when I got a computer with internet access. That's where I went. And that's where I found the first nonprofit devoted to the kinds of problems like I had. And so I just think they're wonderful and they certainly are an excellent resource for lots of people.

Health Hats: Thank you. Thanks. This has been great. I appreciate your time.It's been great. We'll meet again.

Doug Lindsay: I may have to interview you one day because I did all the talk.

Health Hats: Let me know I'm at your service.

Doug Lindsay: Thank you so much, Danny. Take care. Bye.

Reflection 33:07

Thanks to Doug for summarizing. I especially, like *Rare Doesn't Mean Never.* Good news for us all! Doug's public comment about rare disease as an equity community was heard by PCORI. Good news for me. Podcasting, mainly the interviews, introduces me to many new ideas and fresh personal stories. Editing the audio and transcript imprints the gems for me, counter-balancing my usually swiss cheese brain – forgetting as soon as the interview ends. My gratitude percolates through my brain feeding my drive to continue connecting dots, networking, and advocating. Onward