

RARE-Xtra Podcast - *Creating a Faster Path to a Rare Disease Diagnosis*

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Podcast Description: Despite a growing number of diagnostic tools, it still takes an average of six years after symptom onset for a patient with a rare disease to receive an accurate diagnosis. A recent report from the pharmaceutical company Takeda identifies three priority policy reforms designed to address the barriers patients with rare and genetic conditions face in getting a diagnosis. The report “Reducing Time to Diagnosis for People Living with Rare Diseases: A Conversation on U.S. Policy Opportunities” offers solutions that are designed to address persistent and long-standing barriers that contribute to an ongoing cycle of missed or delayed diagnosis and treatment for patients. We spoke to Takeda Senior Vice President of U.S. Rare Disease Cheryl Schwartz and RARE-X CEO Charlene Son Rigby about the report, the recommendations it makes, and what it will take to turn these ideas into action.

Transcript

Daniel Levine: I'm Daniel Levine, and this is RARE-Xtra.

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Despite a growing number of diagnostic tools, it still takes an average of six years after symptom onset for a patient with a rare disease to receive an accurate diagnosis. A recent report from the pharmaceutical company Takeda identifies three priority policy reforms designed to address the barriers patients with rare and genetic conditions face in getting a diagnosis. The report, Reducing Time to Diagnosis for People Living with Rare Diseases: A Conversation on U.S. Policy Opportunities, offers solutions that are designed to address persistent and long-standing barriers that contribute to an ongoing cycle of missed or delayed diagnosis and treatment for patients. We spoke to Takeda Senior Vice President of U.S. Rare Disease, Cheryl Schwartz and RARE-X CEO, Charlene Son Rigby about the report, the recommendations it makes, and what it will take to turn these ideas into action.

Cheryl, Charlene, thanks for joining us.

Cheryl Schwartz: Thanks for having us.

Charlene Son Rigby: Great to be here.

Daniel Levine: We're gonna talk about a recent report from Takeda on the diagnostic odyssey for rare disease patients and its proposals for reducing the time to a diagnosis. Cheryl, perhaps we can begin with a problem. Why is it difficult for rare disease patients to get a diagnosis?

Cheryl Schwartz: Well, first of all, thank you so much for taking the time to speak today on this really

important topic. I think of course, a big part of the challenge of diagnosing a rare disease is that many healthcare providers don't actually have firsthand experience with these diseases, because they're just so uncommon. So kind of like the proverbial needle and haystack.

Also often symptoms of rare diseases can actually resemble those of more common conditions. So for example, in some childhood rare diseases like MPS II or Hunters disease, as an example, initial symptoms can look more like benign childhood disorders, like hernias or hearing loss, and all too often, this can result in either an incorrect or a significantly delayed diagnosis.

But at the same time, there's also systemic barriers that patients face when it comes to what we call this diagnostic odyssey or journey that's associated with rare diseases. So even though we've seen really incredible advancements in genetic testing and diagnostics, it still kind of amazingly takes on average 17 interactions across the healthcare system, and we talk about this in the white paper, and up to six years to get a rare disease diagnosis. And there are some disease areas that we work on here at Takeda, areas like hereditary angioedema, as an example, where we've actually heard stories of patients living without a diagnosis for far longer than that, even up to decades in some cases. So unfortunately this is a pretty common challenge for the many millions of Americans that are living with a rare disease.

Daniel Levine: What's the consequence of that delay? What does this mean for patients and their families?

Cheryl Schwartz: Of course, a protracted path to a diagnosis, unfortunately also means delays in receiving care and, and the treatment that can be life altering or even potentially lifesaving. You know, in some cases rare diseases can be degenerative, so, you know, a delay in a treatment can actually lead to a decline in physical functioning or neurocognitive functioning. In other cases, it can really significantly impact the quality of life for patients and their families. As a parent, I often try to imagine what that must be like, you know, going through this diagnostic odyssey with your kid and not knowing what's wrong with them and, and living with that and, and the stress of that within your family system and your community.

And then there's also this broader societal issue beyond, you know, the individual impact of the, the economic impact of a disease, both at the family level and at the societal level. You know, there are thousands of rare diseases. So even though we talk about concept of rare, sometimes we don't really fully appreciate that there's an estimated 30 million Americans, that's one in 10 people that live with, with a rare disease. So while individual diseases could be rare or even ultra-rare, on aggregate a recent study by the EveryLife Foundation for Rare Diseases found that the total economic burden of rare diseases in the US approached \$1 trillion in 2019. And that's in addition to the really significant toll that it takes on the individual family and community level as well. So, really the consequence of this delay is significant.

Daniel Levine: Oh, what was the idea behind end this report? How did Takeda come to focus on this issue and, and what's it trying to do?

Cheryl Schwartz: Yeah. That's a good question. At Takeda, we've been working in the area of rare disease for many, many years and, you know, we have a very strong commitment to rare disease communities. But that commitment expands beyond the development of innovative new treatments, to working with partners globally, to do a few things, to, to reduce barriers, to improve the diagnostic journey. And ultimately our goal is to reduce the complexity and the time to diagnosis and treatment so that people can have the best possible outcomes. So calling attention to these issues that are outlined in the report and that many of us who work in the rare disease area grapple with every day was really the intent of the white paper and ultimately why we think it's so important to work with healthcare stakeholders and institutions with patients and advocacy groups in the rare disease space on very actionable policy changes that we believe can have a real and lasting impact on improving the situation overall.

Daniel Levine: The report identifies what it calls three opportunities for high impact solutions. I'd like to walk through each of those. The first of these is widespread and equitable access to genetic screening. We've got newborn screening tests that can identify rare disease at birth, but in many cases, what test an infant may receive depends on what state a child's born in. And even then there are far more diseases that can be detected today than these tests actually seek to identify. What can be done to address this gap?

Cheryl Schwartz: Yes. The lack of equitable access to genetic screening options, both at an early age in terms of newborn screening and also further on into adulthood is a big barrier for a lot of people with undiagnosed conditions in this space. We know absolutely that screening newborns, for example, can help to save lives and improve the quality of life, by helping to support early diagnosis and treatment.

At the federal level, um, there's something called the RUSP, which is the Recommended Uniform Screening Panel, which sets these national recommendations for conditions that should be screened for at birth. And I, this is something I didn't know until I started working in the area of rare disease, is that actually every state actually implements its own newborn screening program independently. So they make their own decision at a statewide level on what to screen for, you know, using the recommendations, but this can create variability, geographically in terms of the type of screenings and an inherent disparity in terms of access and care on a state by state level.

So that's something that, you know, really it, has a big impact in terms of the level of screening that, that can be expected, um, at a state by state level. But, you know, beyond that, it's not just about newborn screening, although that's certainly a critically important component, you know, even in older patients, and certainly there's could be a lack of awareness or lack of access or funding for genomic screening or even genetic counseling, that can make it really difficult to identify later onset conditions. I think this is especially exacerbated in underserved

populations or communities of color who might already be facing underlying challenges to accessing even routine health screenings because of the inequities that exist within our, our healthcare system more broadly.

So I think expanding federal requirements for genetic screening, certainly including newborn screening and, and genomic sequencing and ensuring some consistency across the states would help to expand our knowledge base, understanding of rare diseases. It would certainly be a source of rich data and information to guide future decision making and, and ultimately would help improve the standard of care for patients. So our vision, certainly as, that, some, one that we share within the rare disease community is a future where a genetic screening is available and accessible for all individuals and families who need it.

Daniel Levine: We've seen compelling evidence that the use of whole genome sequencing for children suspected of having a rare genetic disease can be cost effective and lifesaving, what will it take to expand access to this type of testing?

Cheryl Schwartz: It's funny, I think, any of us who've really interacted, (laughs), with the healthcare system in this country know that any kind of specialized care, you know, can be really fragmented even with the advancement of new technologies, like, you know, whole genome sequencing as an example, which is really, and such an amazing tool at our disposal to be able to help with diagnosis. I think that there's a few different areas that we need to focus on to make this more accessible.

I think one is, you know, really making sure that we have, the right sort of policies and funding in place to support genetic testing or sequencing. I think the other one is to make sure that we have specialized training and awareness of healthcare providers to make sure that they understand when and how to access these technologies. And then there's other kind of ancillary areas that are around, issues like privacy, around making sure that that information can be used appropriately, to guide clinical decision making, but also to aid in sort of the, the more holistic, and aggregation of data, across these rare diseases. So I think that there's a variety of different things that have to come together to make this more accessible. I think the technology is there. It's how we support and enable that technology moving forward.

Daniel Levine: The report also calls for investment in centralized and specialized rare disease care. This envisions the creation of centers of excellence and networks of care. Can you explain what these are?

Cheryl Schwartz: Yeah. You know, centers of excellence, I think are, are pretty variable in the rare disease space. Certainly in the rare disease setting, it's more important than, you know, than really anything else to make sure that families and patients have access to information and not just information, but help to navigate and coordinate a really complex network of medical specialties, and venues to be able to coordinate their care. Now I think that this idea of centralized medical expertise, either through a clinical center of excellence or a dedicated network of care, those things have been shown to really help support a better standard of, you know, evidence

based care for patients with rare diseases. We've definitely seen this work more consistently in more prevalent, rare disease areas like hemophilia as an example. There's been sort of this development of something called HTC's, Hemophilia Treatment Centers, which do kind of soup to nuts all of the care associated with the hemophilia patient. And that's been really successful in terms of helping to manage care and outcomes.

But we definitely need more continued focus on this for other rare conditions that require that level of really specialized training and care coordination. So one really good example of that is the Rare Disease Institute at Children's National Hospital in Washington, D.C., which is a center of excellence for rare genetic diseases. I think in addition to really highly individualized patient care in the rare disease setting, one also really exciting initiative, that RDI has been working on as a collaboration, between Children's National, NORD and Takeda to support something that's called the Rare Disease Clinical Activity Protocol program. We call it Rare-CAP for short 'cause it's a very, it's pretty of a mouthful. And that supports a system that helps to really aggregate and curate data and clinical protocols that will hopefully help to standardize the process of diagnosis and care for patients with some of these rare diseases.

I think that these, this idea of centralized care, very specialized training will really help not just to advance our understanding of these diseases, the evolution of our protocols and our ongoing research, but also help to kind of orient people individually through the care process so that they get the best outcomes possible.

Daniel Levine: Well, how does this qualitatively change the approach to care for someone with a rare disease?

Cheryl Schwartz: I think it could be different for everyone. Certainly on an individual level it could mean you're not wasting as much time navigating a fragmented health system. But instead you're, you're getting more quickly to, to that diagnosis and treatment that we talked about earlier. In other cases, it could mean having access to the very latest research, to clinical trials, to updated treatment protocols or even support services that might not be available in other venues for, for patients and families, because of the rarity of these disease areas. In the case of the RDI Rare-CAP initiative, I was just talking about, what it could mean for patients is this idea of more real time curation of centralization of data to inform clinical decision making. Because that data is so disparate. It is sort of the needle in the haystack. How do you pull that information together to guide decision meeting, decision making and, and speed, to information and decision making?

Daniel Levine: What would it take to achieve this? And, and how would it address the, the geographic dispersity of patients who may not live nearby a center of excellence?

Cheryl Schwartz: Well, I mean, I think and I hope very much that we're on the right path here. I think certainly, optimizing already established health networks, and, you know, centers of excellence. And clinical expertise is one, is one area and that can help to provide individuals with better options when it comes to this idea of more personalized

care and clinical pathways, access to the appropriate diagnostic tools and treatments. But I think maintaining this kind of expertise means us as a, as a society prioritizing both recruitment and training, of the right specialized medical professionals that have that rare disease expertise and training.

I also think we're in a place where technology can certainly help to support this in new ways, whether that is that aggregation and curation of data that we talked about. Data has consistently been a very challenging area for us in the rare disease space, just because it is ... you know, we just don't have the wealth of data that we have in other kinds of therapeutic areas. Um, but even in the last several years, I think with the ongoing COVID pandemic, we've seen some pretty remarkable advancements in, you know, the technologies that can help to support information sharing and patient care. Telemedicine and other innovations, that can help to address these, these issues around, you know, geographic dispersity of, you know, of, of patients and, and really giving patients access to top care, for these very specialized areas.

Daniel Levine: The final recommendation in the report relates to improvement in the data landscape, what makes this particularly critical in the rare disease space?

Cheryl Schwartz: So there's definitely a growing body of data and clinical evidence on rare disease. And we talked a little bit earlier about genomic sequencing and that has certainly been a wealth of information for us in this area that has helped to guide new innovation in this space. But, the information is often again pretty disparate, pretty challenging to access and to consolidate and to interpret. Because it's still the needle in the haystack situation that we're dealing with. I think it's complicated by the fact that we often don't even have this information collected in a consistent way. Like even the terminology that we use hasn't been consistent, right?

So many of these rare diseases haven't been assigned appropriate ICD-10-CM diagnosis codes or maybe they're misclassified or diagnosed. So that results in additional barriers for data tracking and collection. And, certainly we often see that diagnosis is through a variety of different tools, but isn't as straightforward as, as it is in other therapeutic areas. So I think that's one area of focus, which is, I think helpful for, on the data side is making sure that we have consistency in how we characterize this information so that we can build up more reliable and disease specific data around these areas rare disease.

I also think we can really work further on building partnerships to develop more advanced technological solutions. The technology is there, we just have to be able to utilize it appropriately. Whether that is artificial intelligence, that can help to sort of guide us in that diagnostic odyssey that I talked about earlier whether that's around this aggregation of data and really looking for patterns and clues in terms of defining treatment paths for patients. And then I finally, I think I mentioned this a little bit earlier, but also developing some of the frameworks from a policy perspective that help to address, some of the ethical concerns around privacy and data sharing appropriate use of that clinical information or that, that genomic information that I talked about earlier will all be, I think really helpful in supporting

better use of data in the future.

Charlene Son Rigby

You know, frankly, I think this is a moral imperative. Traditionally healthcare systems and studies have generated these silos of data and it's been really difficult to bridge or integrate these data sets. I've been very excited over the past few years to see that there's a growing appreciation that these data sets can't be maintained as silos. If we're going to be able to effectively utilize the data, to understand, and to diagnose rare disease patients.

It's critical to understand that it's not enough to just bring two data sets together. They, the data needs to be integrated in a way that generates useful insights. So utilizing data standards, you know, for example, human, the Human Phenotype Ontology, HL7, you know, OMIM, you know, Cheryl in ICD-10, you know. Even though there are gaps in coverage for a lot of rare diseases, these really facilitate structuring and enable the integration of data across these data sets. To take this a little further, I'll use an example, um, from my previous company. So why is standardization valuable in diagnostics? My previous company, Fabric Genomics develops automated artificial intelligence algorithms that relate phenotype and hold genome or exome data to accelerate diagnosis for rare disease patients. And, uh, you know, a critical input to this is standardized terms specifically standardized phenotype data from the electronic medical record that provides deep phenotyping to facilitate and enable this diagnostic workflow.

Daniel Levine:

The report also notes that there have been policy frameworks and programs to encourage rare disease data sharing. Why is this such a concern today in the rare disease world?

Charlene Son Rigby

As we have just been talking about, we need to really maximize the utility of available data for rare disease populations, and also do it in a responsible way. Understanding patient symptoms, the spectrum of patients, disease progression, all of this type of data really should be pre-competitive. And in the past and today, not sharing data has really slowed progress in these patient populations. And so it's, I think it's critical that, you know, policy really start to enable this kind of sharing. Um, rare disease patients, often experience high healthcare utilization. And sometimes this is even for procedures that would be unnecessary or even inappropriate with an accurate diagnosis, notwithstanding the delays of getting onto the right treatment path. So broad data sharing will accelerate our ability to understand and more accurately diagnose patients and further to develop meaningful therapies for them.

Daniel Levine:

How can we better foster data sharing?

Charlene Son Rigby

A great question. So consents, which start the process for a patient to be a, or participant to be able to provide data really should allow for maximal utilization of the data. And that means that the consent should allow for usage of the data beyond the initial purpose or the study it was collected for. Importantly, this should be done in a transparent way for participants. So at RARE-X we've developed a consent that allows participants to decide how they want to share their data. For

example, for any research, for non-commercial research, it also gives them the ability to stop sharing their data if they were to choose to do that. And this enables patients to be active participants and stakeholders with a real seat at the table in the research process.

From a downstream perspective the data access process for researchers needs to be streamlined and simplified in a responsible way. It really shouldn't take months to request and gain approval for access to data for a project. You know, obviously this delays research progress, and we can even experience situations where researchers may actually lose interest in the project. So we really need to tear down these barriers to research.

Daniel Levine: The report talks about the important role patient organizations can play in changing the rare disease data landscape. What can patient organizations do?

Charlene Son Rigby: Yeah. Well, patient advocates and patient advocacy organizations are critical stakeholders and drivers within the rare disease space. At the most basic level, they're often the first and only people building awareness and initiating researcher interest in a specific rare disease. And that's of course because they or their loved ones are impacted by it. It's often through the dedicated efforts of patient organizations that registries and natural history studies are first established. We feel that patient organizations should work to ensure that in these data collection efforts, data standards are employed and that the resulting data is openly accessible for research.

Daniel Levine: Cheryl, the report also talks about collaborations between patient organizations and other stakeholders. What do you think those collaborations should look like and what role do you see them playing in improving the data landscape?

Cheryl Schwartz: Yeah. I think building up on what Charlene was talking about in my experience most often, it's the patient organizations that are most often at the forefront of not just, you know, advocacy, but, and change, but in terms of that data and information. Patients and their families and their communities are often have more information than, than even the researchers themselves. And maybe they're looking at this disease from different angles and different levels of awareness. So I think first and foremost as advocates in this space helping to guide the appropriate collection of information, making sure that we are, that we're holding ourselves accountable, um, to, you know, what these patients are living with every day and that we're collecting the relevant information. Sometimes we get so caught up in the drug development process in, in terms of what regulators are requiring.

Sometimes we go so far down the path of information that we're collecting to seek a regulatory approval that we're missing really critical information potentially that could guide decision making or care for some of these communities. And so who better to be able to understand that than, than patient organizations. So I think that that's one part.

I think the other part is around, you know, really about again, where Charlene was

coming from this idea of transparency and, and trust. I think we, people who get involved in the rare disease space do so because they, they have a real passion and to these communities. But we have to make sure that we're operating in a way that we're protecting confidentiality and privacy, but also advancing kind of our research objectives and our objectives around advancing treatment.

Daniel Levine: Takeda has laid out an agenda to reduce the time to diagnosis for rare disease patient. What comes next? How do you turn this into action?

Cheryl Schwartz: Yeah. I mean, it's definitely a big task. I guess I would come back to that statistic that I mentioned, you know, earlier, which is 30 million American or one in 10 people live with one or more rare diseases. That's kind of a, it's just staggering every time I think about that, because it just doesn't fit with the title rare. So it's really important to those 30 million people and to, you know, all of us at Takeda, um, I know to, to Charlene as well, (laughs), you know, everyone that interacts with these communities every day, that we really help to drive action to support the appropriate legislative and regulatory changes at both the federal and the state level to support this idea of reducing time to diagnosis for rare disease patients and their families.

So we, we talked today about some of these actionable areas that could help to shorten the time to diagnosis. One is certainly ensuring access to genetic and genomic screening. That is a, a wonderful tool that we have at our disposal. But that includes things like expanding access to newborn screening both at the federal level, but also state policy makers are a big part of that solution. You know, that could mean advancing legislation or funding to support that enhanced screening, um, or new diagnostic tools, but also then to be able to use that, that screening and that data to support kind of the information that guides us for the future.

We're also really focused on this idea of enhancing the appropriate collection, curation and standardization of rare disease data, both through the centralized and specialized rare disease care, through centers of excellence but also by improving the data landscape around rare diseases as we were just talking about. So I think that's a really critical piece of the puzzle that needs to continue to be advanced. I think all of these are really important and actionable steps. We're very committed here at Takeda and within the broader rare disease community to working with partners and, and key stakeholders to advance these kinds of solutions to best support rare disease communities.

Daniel Levine: The report is Reducing Time to Diagnosis for People Living with Rare Diseases: A Conversation on U.S. Policy Opportunities. You can find the report on the Takeda website under the, What We Do tab looking for rare diseases.

Cheryl Schwartz, Senior Vice President of Takeda's rare disease business, and Charlene Son Rigby, CEO of RARE-X. Charlene, Cheryl, thank you both.

Charlene Son Rigby Thank you.

Cheryl Schwartz: Thank you so much.

Daniel Levine: Thanks for listening. RARE-X is a collaborative platform for global data sharing and analysis to accelerate treatments for rare disease. RARE-X is adapting proven technologies and partnering with leading experts to create a federated data analysis platform, specifically designed by rare community leaders scale to support the diverse and expanding needs of rare disease research, development, and care. To learn more about RARE-X, go to rare-x.org. This podcast is produced for RARE-X by the Levin Media Group. Music is courtesy of the Jonah Levine Collective.