

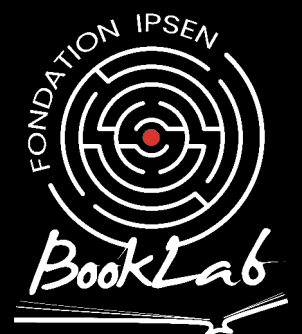
The Rare Disease Gazette

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

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**BRINGING
CARE TO UNDERSERVED
POPULATIONS**



Editorial

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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 2022, these webinars focused on building solutions to improve the detection of rare diseases. *The Rare Disease Gazette* is a magazine that broadcasts these discussions.

James Levine



DON'T MISS!

The Conversation

Experts of the month: Sean Sanders, PhD, hosts a conversation with world's experts about bringing rare disease care to underserved populations

The Conversation

Experts of the month

Nakela L. Cook, M.D., M.P.H. (*Patient-Centered Outcomes Research Institute (PCORI), Washington, DC*)

Linda Goler Blount, M.P.H. (*Black Women's Health Imperative, Atlanta, GA*)

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

Jamie Sullivan, M.P.H. (*EveryLife Foundation, Washington, DC*)

Consuelo Wilkins, M.D., MSCI (*Vanderbilt University Medical Center, Nashville, TN*)

Sean Sanders (host):

A very warm welcome to this fourth webinar in our 2022 "Science and Life" series on rare diseases, entitled Doing better where it counts: Bringing rare disease care to underserved populations.

Consuelo Wilkins:

I am Consuelo Wilkins. I am the Chief Equity Officer and Senior Associate Dean for health equity at Vanderbilt University Medical Center. I am trained in internal medicine geriatrics, although I now spend most of my time focused on research that emphasizes health equity, which is relevant to today's discussion. I am one of the leaders of a recruitment innovation center that provides guidance and resources around clinical trials, including those for rare diseases.

Linda Goler Blount:

I am Linda Goler Blount, President and CEO of the Black Women's Health Imperative. The Black Women's Health Imperative is the only national non-profit organization focused on Black women's health, and has been for almost 40 years. I am an epidemiologist by training, and we focus on chronic disease prevention, reproductive justice, maternal health, and we have a significant policy shop. I think for the purposes of today's conversation, it is worth mentioning that I am the Chair of the Rare Disease Diversity Coalition (RDDC), which is a coalition of more than 50 pharmaceutical companies, patient advocacy groups and research groups that are focused on trying to understand the drivers of inequities in rare disease, treatment and diagnosis, and to shorten the amount of time from appearance of symptoms to diagnosis to effective treatment, and to improve the research pipeline for rare disease. So, I am happy to be here, and I am looking forward to the conversation.

Nakela Cook:

I am Nakela Cook. I am Executive Director at the Patient-Centered Outcomes Research Institute or PCORI. PCORI (<https://www.pcori.org/>) is a research funding organization that targets the opportunities to provide research funding for studies that will help empower patients and other stakeholders, such as caregivers, clinicians and policy makers, with the information and evidence that is needed to make important health care decisions. We do this by funding comparative clinical effectiveness research or CER, as you may hear me call it today. One of the unique things about PCORI is that our authorizing law emphasizes research for rare diseases. In doing so, it authorizes the establishment of an advisory panel for rare diseases that PCORI taps into to understand the issues important to conversations like today for patients that may be across the country. I am a cardiologist and a health services researcher by background. I have had a long-standing interest in addressing the issues of differential outcomes and health care access as well as health outcomes amongst individuals that live in different parts of the country, may have differential access by geography, as well as by race, ethnicity, sex and gender, and other issues. This intersection, of thinking about those individuals with rare diseases that may particularly live in underserved communities, is incredibly important to me.

Jamie Sullivan:

I am Jamie Sullivan. I am the Senior Director of Policy at the EveryLife Foundation for Rare Diseases. EveryLife Foundation is a non-profit, patient-focused organization. Our mission is to bring innovation in the diagnostic odyssey, and to improve the development of an access to treatments and diagnostics. I work on our regulatory and legislative initiatives. I really look forward to this panel discussion where I can talk about some of the work we are doing in collaboration with groups like Linda's to help track policies that can not only support innovation in rare diseases, but also help address the underserved, under-resourced populations that we are here to talk about.

Sean Sanders (host):

I think it would be helpful to start with what we mean by underserved populations, or under-represented populations, particularly those that are dealing with rare diseases. Consuelo, how do you see this population? Where are they and what challenges are they facing?

Consuelo Wilkins:

I think it is important to start with what we are talking about. The term "underserved" itself is a broad term. There are many reasons why populations, or communities, might not be served. I think it is important to contextualize: are we talking about populations not served by the healthcare system, the health delivery system, people not served by research, or people not served by the social and structural support systems that many of the populations we are talking about are really suffering from, being disenfranchised, marginalized, minoritized, disinvested? We should try and define specifically which populations we are talking about, otherwise, people might be imagining very different things. When I am talking about these groups, I try not to use the term "underserved" unless I am specifically talking about healthcare utilization or services. I am more frequently talking about groups that have been minoritized due to their race or ethnicity, social circumstances, and other identities.

Sean Sanders (host):

Thank you, Consuelo. I wanted to add that when I think of underserved populations, I also think of populations in countries that don't have the same access to healthcare that some Western countries have, particularly those living in very rural communities who might be a day of travel away from medical care. Nakela, do you have any other thoughts on the subject?

Nakela Cook:

I would love to give a perspective related to research itself and thinking about the populations that we are talking about when we think about health research. One of the things that we have talked quite a bit about with our advisory panel on rare diseases is that we are often in a situation where those that may have rare diseases have been historically excluded from a lot of the clinical research studies that are undertaken. This is predominantly because either it may not be recognized what symptoms and constellation of symptoms may be presenting with the rare disease, or that such individuals may have other complex health issues that may not have them included in traditional research studies. Therefore, those with rare diseases are historically excluded populations.

“Those with rare diseases are historically excluded populations.”

I will also mention that we typically have focused on patients with rare diseases who also live in communities where they may not have access to traditional services, when we talk about utilization of services and underserved. We also recognize that those patients who live with rare diseases may be members of communities that could potentially be defined as not having those access to services, and that could really be considered as “underserved” by definition. So, we broaden the thinking about the access to services and the utilization of services, and, as Consuelo mentioned, about potentially the way in which we think about marginalized populations.

Linda Goler Blount:

Just so people don't get the impression that “underserved” is a passive experience, I would add that in fact, in this country and outside the US, it can be very deliberate. As we look at the effect of ‘redlining’, which is the systematic disinvestment in certain communities that makes access to quality public schools very difficult, and that keeps people from being able to own homes in neighborhoods that might be closer to academic medical centers, there are many examples of systemic policies that have harmed populations by race, by ethnicity, by income, and obviously by geography. The term “underserved” contains a deliberate attempt to make sure that certain populations don't have access to the kinds of care, research experience and quality outcomes that we are talking about today.

Sean Sanders (host):

Thank you for making that point, Linda. Jamie, I would like to turn to you to talk broadly about some of the challenges that are faced by rare disease communities, patients and families. Following that, we will talk specifically about how we layer on top of those challenges the challenges that we have just been talking about for minoritized and marginalized communities.

Jamie Sullivan:

Broadly, one of the challenges that we focus on is the diagnostic odyssey and the

fact that rare disease patients on average face about a 6.3-year diagnostic odyssey after the initial symptoms have presented and they have sought care. It takes an average of 16.9 different physicians just to get a diagnosis. Keep in mind that these numbers are coming from a study of people that made it through the process, who made it through the diagnostic odyssey. When we know that there are countless numbers of individuals who are still facing that odyssey and who are not connected into the system to even fill out a study, or a survey like this, 6.3 years and 16.9 physicians is perhaps the best-case scenario.

If they are able to obtain a diagnosis, then we see some challenges around access to care. That starts with our systems that aren't generally set up to count, track and help connect rare disease patients to the right resources. One challenge is that only a small fragment of rare diseases has diagnostic codes, and that leads to issues around access to care, prioritization, and connecting the patients into the research opportunities that might be there. It also includes the fact that there are only about 5% of rare diseases that even have treatment options. Another broad challenge faced by rare diseases is the fact that by and large, there are no treatments that have been approved, and so the care that they can access consists of leveraging treatments for symptom mitigation that might be used in other conditions. They also may not even be able to do that because the specialist care is not available for many rare disease patients. We can go into more depth in any one of these areas.

Another challenge is that we have care from specialists that is inaccessible, because there are simply very few specialists in many rare diseases. Generally, people talk about over 7,000 rare diseases, but more and more evidence is coming to light that there are actually over 10,000, and more are identified every day. The patients facing rare disease diagnosis are trying to navigate a system that is not built for that level of specialty care, and certainly not, if they are living in rural areas, not already connected in with the healthcare system. These are just a few of the many challenges that we focus on at EveryLife.

Sean Sanders (host):

Great, thank you for outlining these challenges, Jamie. Linda and Consuelo, hearing all of these challenges, can you provide us a sense of how these populations that are marginalized, under-represented and underserved experience the rare disease odyssey? What addi-

tional challenges might they have, for example, both when getting access to care and figuring in mistrust of doctors in some communities or language issues in certain other communities..?

Linda Goler Blount:

For patients of color in particular, the diagnostic odyssey, as we call it, can be on average 7 to 12 years. This partly has to do with access, but part of it is also their relationship with their providers. Oftentimes, providers of patients of color don't think about rare diseases. I think that may be true in general: as it is rare, it may not occur to providers. However, through the RDDC, a couple of examples of patients come to mind. A man was diagnosed with cystic fibrosis at the age of 52 after decades of symptoms. It took that long for providers to finally decide that it might be cystic fibrosis. Another had a rare kidney disease. His doctor told him, “You need to stop eating fried chicken.” He is actually a vegan, he had never had fried chicken. There are some things that just never occur to physicians, but we can't make it the patient's responsibility to understand or diagnose him or herself. As you talk about mistrust, we see that once these patients finally got a diagnosis, they can then go back, re-play their experiences and realize how they had been underserved and disrespected along the way.

When we think about what we do to create evidence, of course, the first reason why people of color don't participate in clinical trials is that nobody asks them. It is not because they distrust the system, that is a part of it, but they are just simply left out because providers make assumptions about what they will and will not do and what their adherence would be. Of course, there are a myriad of other barriers around transportation, costs and these sorts of challenges. But what we are hearing through the RDDC is that the providers need to step back and consider for patients of color, for low-income patients, things that they might not ordinarily consider, to give them the opportunity to begin that process and hopefully shorten that time period.

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just simply left out because providers make assumptions about what they will and will not do and what their adherence would be. [...] Providers need to step back and consider, for patients of color, for low-income patients, things that they might not ordinarily consider, to give them the opportunity to begin that process and hopefully shorten that [diagnostic odyssey] time period."

Jamie Sullivan:

To reinforce what Linda was saying, in a recent study that came out, they did universal whole genome screening of babies that were in the NICU and were experiencing some types of symptoms that hadn't been identified. They then went back and looked for those babies that weren't previously recommended for genetic testing, but who should have had genetic testing. They found 67% of the group that had never been recommended for genetic testing were non-White populations. The paper was out of Seattle, it was talking about the fact that there is potentially an inherent bias by clinicians, against thinking about genetic diagnoses in non-White populations. That is a huge barrier for rare disease patients to get an accurate diagnosis.

Consuelo Wilkins:

Perhaps I will frame my points based on Jamie's description of how the system isn't structured and prepared for patients with rare diseases. Imagine that also, for many of these populations that have been disinvested, marginalized and minoritized, the health delivery systems, the research, clinical research operations, were not designed with these groups in mind. The impact of this is exponential. We have rare diseases on the one hand, and we have a system that was not designed for these individuals on the other hand.

"We have rare diseases on the one hand, and we have a system that was not designed for these individuals on the other hand."

I would also like to echo Linda's earlier point about some of this being intentional: we do not want to dismiss or forget that racism, discrimination, and bias built these systems that we are talking about. These are the same systems that historically excluded people from research, excluded people from high-quality healthcare, segregated care... All these things are built into the foundation of healthcare delivery and research. That can't be forgotten. We can't just presume that people don't want to participate: they are not being invited. Also, we have to recognize our role as researchers, clinicians, systems builders, and elected officials. Everybody has a role in what we have created here.

The other point I will make is the need for cultural humility. Again, we have people who are presenting with symptoms that might not be clear. The constellation might not be clear, but there is also a lack of humility when we are talking to people who might be presenting even with slightly different symptoms than those that we are already aware of for some of these rare diseases. So, the barrier is not necessarily the language of the individual patient or family, but it is our lack of ability to provide appropriate care services, interpreters, etcetera. I am very big on reframing this. It is not the mistrust or distrust of the population, it is the lack of trustworthiness of our systems of healthcare and research.

"We do not want to dismiss or forget that racism, discrimination, and bias built these systems that we are talking about. These are the same systems that historically excluded people from research, excluded people from high-quality healthcare, segregated care... All these things are built into the foundation of healthcare delivery and research."

Nakela Cook:

I may just add one other point here, which relates to the specialty care that is unique and needed for patients with rare diseases. I think another compounding factor, when you start to think about populations that have been historically excluded, marginalized or minoritized, is that the access to those specialty care centers, special-

ists, etcetera, has already been shown not to be as robust and to be a challenge, especially for our chronic conditions that really require it. If you then compound what is needed for rare diseases, I think this becomes incredibly important, because referral to centers that have specialized care is essential in the care of rare diseases. Being a cardiologist and thinking about specialty care, I just wanted to underscore this other additional important factor about our healthcare system, as it relates to people of color, people that traditionally don't have access to these types of services on a routine basis. Having this sort of need, really makes it a much more complicated scenario for them.

Sean Sanders (host):

Nakela, could you please talk about some of the challenges of doing research in rare diseases and including people of color and people from these under-represented communities?

Nakela Cook:

Sure, I think it is an important question for us to talk about in terms of research with rare diseases, because many have focused on the fact that there aren't treatments available for 95% of the conditions that we now think about in terms of rare diseases. At PCORI, we have focused on a research portfolio in the space of comparative clinical effectiveness research. I will give you a couple of points about why it is even harder in that scenario. We have a portfolio related to about 40 different comparative effectiveness research studies and methods studies – methods, because it is important to understand how you reach patients and individuals with rare diseases that may not necessarily be concentrated in one specific area, etcetera. You must think about how you reach them across the nation. Our studies have predominantly focused on those that have been priority populations such as racial and ethnic minorities, women, older adults, people with disabilities, or even those that may be in these underserved areas of the country, or potentially even those in those marginalized communities where there may be a lower level of literacy or numeracy.

We learned a lot from this type of research. We traditionally have found that sample sizes are a real challenge for very robust studies where you need a certain number of individuals to give you the kind of definitive results that may help to inform a treatment change in the clinical guidelines or clinical care practice. When you start to

think about comparative effectiveness research where we typically compare more than one known intervention that can be efficacious, we often find that for rare diseases, there aren't such interventions and very few to compare. So, we have had to go back to ground zero and think about some of the ways to address sample size challenges as well as try to figure out the types of things that may be in use that we could understand more about. One of the resources that we have used is a research network that is called PCORnet, that PCORI funds, to try to overcome some of the sample size challenges. It has a reach to many patients, electronic health record data and other types of sources, for us to observationally review what is happening in the treatment of rare diseases.

We have focused on comparing treatment modalities, or treatments with cross-cutting symptoms or screening practices. We are looking at treatments for cross-cutting symptoms that may be common among groups of rare diseases, to try to overcome some of those hurdles. So, we know that things like sleep disturbances, or pruritus, or comorbid other conditions can be common across rare diseases, and we are hoping to find clues there that could stimulate the discovery pipeline. So, it is a challenge in terms of thinking about research for individuals with rare diseases, and compounded on that are the challenges that we traditionally have in trying to engage populations that have a lot of competing priorities related to their health, healthcare, and daily survival. We recognize that and use some special strategies around engagement that I can talk about a little bit later as well.

Sean Sanders (host):

Nakela and Consuelo, thinking about communities with food insecurity, high rates of poverty, or countries that are struggling simply to feed a large percentage of their population or are fighting communicable diseases, what are the reasonable expectations for funding and support of rare disease treatments?

Consuelo Wilkins:

When we are talking about people who are experiencing food insecurity, lack of economic opportunities, or other issues linked to social needs, there are many, many challenges. One of the challenges is that for many of them, it is hard to imagine what is the most important issue for them. They may delay to even present with their

symptoms. People have, for many, many years, symptoms that might not necessarily be mild. They might be disrupting their lives, but their lives are so complex because of the structural and social barriers that they have to overcome. If you don't have food to eat, then you are not necessarily thinking about some symptoms that might be classic, such as mildly short of breath. If you think about Maslow's hierarchy of needs: what do I need at this very minute? Those are often quite challenging, but then they also co-exist with underinsurance, uninsurance, or other issues around access to care.

I would also like to re-emphasize Nakela's point about access to specialty care being so critical and important, not just for people who don't have insurance or are underinsured: having access to an insurance card is not equivalent to access to care. For example, the insurance card doesn't overcome the issues around access, such as if specialty care is in a part of town that is difficult for you to reach because you don't have transportation, or if you cannot take time off work without losing money, or if it is at an academic medical center where all of the historical abuse related to research and clinical care occurred... I think that is one of the biggest hurdles we have. Often, when we are applying for research funding, we are putting in costs for providing meals for people, even just for the day of a research study, but we are often heavily scrutinized and asked to take that out. We are overlooking the fact that participating in research costs an individual. So now, we are asking them to pay with their time or resources, but we don't provide anything for them! We have been able to do things like provide transportation to and from those appointments around research, but again, that is just a small piece of what people need to be able to survive. It would be great for us to be able to think more broadly about what people need to be able to participate in research. And of course, more broadly, what does health look like? And it is not just about a prescription or what happens in the clinical setting.

Nakela Cook:

One of the things I think is an opportunity to overcome some of these big hurdles is to really look to those who have lived experience with these challenges, to inform us on the best path forward. This is really where the work that I described as engagement comes into play. One of the things we hear at PCORI, where we really focus on engagement and patient-centered research, is that engagement of the

patients, caregivers, and these communities that we are talking about, are really important in terms of understanding those affected and understanding what is really desired in order for them to be able to participate in clinical research or clinical care. The different settings where this may occur may need targeted strategies that are specific to certain people, certain populations, and a real understanding of those competing priorities that they are facing in their everyday life.

Many of the awards that PCORI has made that focus on rare diseases come from our engagement award portfolio, because we found there that individuals and communities, who often are thinking about these types of challenges, are looking for opportunities to bring people together in special convenings to talk about the treatments for diseases that may not be available to them immediately, but how they may access them, to think about patients and caregivers that are interested in developing communities of support and for advocacy purposes, and to help identify the research priorities that then we can pursue. Doing that through an engagement venue, I think, is a phenomenal approach.

One example is a sickle cell disease network project that we funded in Tennessee, which was an engagement project. The goal was to try to build capacity for individuals that were living with sickle cell disease throughout Tennessee to engage in research and patient-centered research as well as to try to build a sustainable sickle cell disease network in Tennessee that could serve as a conduit for driving patient-centered research and a health-care service agenda. The outputs were the creation of a rural-urban sickle cell disease community-based network and a facilitation of different educational training sessions on research for non-research stakeholders (those that wanted to be engaged in research but weren't researchers, so to speak). Another output was a patient-centered conference on advocacy and implementation of outreach methods that were created by the community network. This is where, again, hearing a lived experience allows those that we are trying to understand that experience for to benefit from the research and other activities that we are supporting. The value is determined by them, and the engagement and activities allowed us to understand the research agenda that we could then pursue moving forward. I would be happy to talk about some of those other lessons learned from this type of engagement as we go through the conversation.

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Linda Goler Blount:

If I could just amplify what Nakela and Consuelo were saying... We happen to be a grant recipient of PCORI for a program we created called TEACH, Trained Empowered Community Health Advocates. The purpose is to understand the lived experiences of Black and Brown women to help them better negotiate and understand what the clinical trials process is about: how to participate in a way that is respectful, where you feel valued, because we were hearing that those who happened to participate felt like they were being tolerated in many cases. So, understanding the lived experiences and building that into a training program has been really helpful. The RDDC is very much focused on understanding what that experience is like. The informed consent process, for example, is probably burdensome for most participants, especially for low-income participants and participants of color. It is designed to protect the institution. Maybe there is an opportunity to rethink how to make it less burdensome for clinical trial participants. Of course, we must look at the pipeline: the percentage of Black and Brown researchers and those who have received R01 funding from NIH hasn't changed in 40 years. The FDA has some diversity guidelines around clinical trials and research, but they are not enforced. We therefore have some opportunities to make some changes to help broaden the tent, and to make people feel more included and valued. If they do, I think the outcomes will be better.

Jamie Sullivan:

I will add that our policies in the US aren't set up to facilitate easy participation in research. We don't have great paid leave, we don't pay caregivers for the work that they are doing, we don't have great home care coverage or even childcare. We hear from patients who simply can't take another day off work, or their caregiver can't take another day off work. We hear from patients who have two children, one of whom has a rare disease, but they can't go participate in a day of research at the

clinic without a place to bring their second child. Our system and our federal policies or state policies aren't set up to even help, once we can overcome the barriers that you have heard about from Nakela, Consuelo and Linda.

Sean Sanders (host):

We have spent quite a bit of time talking about these barriers and these challenges. I would like to turn to what is working. Linda, what are some good models and good examples of what is working? Where can we look to find those models that we can apply elsewhere? Are those models portable?

Linda Goler Blount:

I wish I could say there were dozens. I probably can't do that, but there is some hope. I mentioned the TEACH program, but there are also examples of academic community partnerships. We worked with a group out of San Jose, California, on something we call "Tech to Equity", where we wanted to bring research to address the needs that the community had defined rather than the needs that researchers had defined. So, the community group in San Jose conducted its own health needs assessment, and they went to the research community in California and Santa Clara University and a couple of other universities to say: "Here are the issues that are important to us, here is what we think needs to be done to help improve outcomes and the overall health status in these communities". This isn't rare disease-specific, but it certainly could be applied in the rare disease space, as advocacy groups come together to help identify the issues and talk about their own experiences. It would take researchers and academic institutions to be willing to listen to them, to value their opinion, to take their own sort of fundamental research seriously and then act on it. So, it is possible, but we would have to see a change in the standard approach to academic research so that the community is included, valued and seen as a part of coming up with solutions to their own concerns.

People have heard me say advocacy is a luxury. You must have time and money to be able to be an advocate. Oftentimes, Black and Brown people and low-income people end up being marginalized by researchers and by clinicians because they are not out there advocating. As we have heard, they have got to work, they have got childcare responsibilities, they may have other responsibilities. They sim-

ply don't have the time or the resources, which doesn't mean they don't care deeply, but they don't have the luxury of the time and the money it takes to be an advocate.

“Advocacy is a luxury. You must have time and money to be able to be an advocate.”

Jamie Sullivan:

I will talk a little bit about one program that I think everyone points to, which is probably the most equitable public health program, although it has a lot of room for improvement: that is newborn screening. You could say similarly about some of the new initiatives that have started to pilot, universal whole genome sequencing for certain populations such as NICUs that have unexplained symptoms. But newborn screening is often held up as one of the most successful public health programs because it is supposed to be universally accessible to every baby born in the US. Truly it is a great success. However, there are certain areas where we know we can still do more and do better.

One thing that Linda just said stood out to me in that you need resources and money to be an advocate. Well, one of the ways the newborn screening system is set up is that the Federal panel makes recommendations on what conditions to include. That nomination process takes over a decade, it often must be led by patient advocacy organizations who then need resources and champions on their side to help get them through that process. Once the federal panel finally says, "Yes, we think this condition should be added", it requires advocates to go state by state and advocate for their condition to be added to the panel. Just the process to get this condition added to the panel can have some inherent inequities in it.

Also, while every baby should be screened, that doesn't mean that every baby has the same chance at benefiting from the care and the therapies that are available following the screen. So, we have a lot of room to improve in the follow-up services in how families are connected to care, and what is available in terms of culturally competent care. Genetic counseling is a great example: genetic counselors, who listen to rare disease patients, are so critical to help them understand and start their journey, and try to find treatment and understand what it means for their family.

And yet, only a very tiny fraction of genetic counselors is coming from the non-White population. There is a ton of room to do better, but I do want to say that newborn screening is certainly a good model, a beneficial model, but I hope that we can all work together to make it as beneficial as it possibly can be.

Consuelo Wilkins:

I would say advocacy is often a luxury and for the privileged. I have worked with a number of really amazing advocates, especially parents. Particularly, often, they are mothers of children with rare conditions; this is their entire life. They spend almost all their time doing it, and not everyone can afford to do that. It is very challenging for those who are doing it, but to do the work, you must have at least the chance of being supported in some other way. They are often people who have a higher level of educational attainment, they have been able to negotiate access to different circles. They can get their talking points together; they go sit in front of their elective officials...

There are so many things that have been set up there, but I will credit PCORI for really helping to shift this in many ways, because bringing the spotlight to the attention that these roles need to be paid, especially when we are partnering, and that people need to be compensated, is something that many advocacy organizations have just not done or even embraced. It is like, "no, no, all of the dollars we raised need to go to the research", and we are not always thinking about who is being left out.

Also, to emphasize Jamie's point: we can advocate for these resources and screenings, but not everyone can benefit the same way. It is not just about access to care and services. If we start doing broad whole genome sequencing on newborns or whomever is presenting, we must be able to tell people that if you are from a population who is not of recent European ancestry, then the likelihood that you are going to have variance of unknown or undetermined significance is going to be much higher. Our history with not having equitable and inclusive research is making it even more challenging for these populations as we move forward. What does that mean for how we do this research? Are we going to build in strategies and plans for when we do have more evidence and understand what these variants mean or might mean? Are we re-contacting families? How often are we going back into the databases to see what else we can glean and learn? Who is communicating that information to these populations? How can they have access to it? There

are lots of other things that we need to build into the structure to try to repair the damage, the historical and ongoing exclusion of these populations. We must work on that.

Sean Sanders (host):

Great, thank you so much. Nakela I would like to give you an opportunity to speak as well. I know it is in your wheelhouse.

Nakela Cook:

Certainly. Firstly, I would like to add something related to one of the points I mentioned before in terms of some of the lessons that we have learned that have worked when we talk about engaging these populations in research that have a lived experience that we can learn from. One of the things that we talk about with engagement as a model is that it is inclusive in identifying the research priorities that are important to a specific population, as well as involving them in the conduct of the research and in the dissemination and implementation of the research findings. Over the last 12 years or so, we have learned that engagement gives the opportunity to make the clinical research reflect the needs and the values of the patients, the caregivers, the clinicians, and other stakeholders. We have learned the importance of compensating people for this type of engagement to allow their voices to be heard and to see them as equal partners in the research enterprise. I think that is incredibly important for making sure that this is considered to be a valuable opportunity for those that were trying to benefit with the work that we are supporting.

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We have also learned that engagement and research helps to improve the feasibility of doing this type of research in real world settings. As it relates to rare diseases, one of the things we talked about were some of the challenges of sample size for research. Moving into real world settings or trying to figure out how to do that when you are dealing with the issues of transportation, childcare, the competing issues of costs. We know that individuals with rare diseases have much higher medical and out-of-pocket costs and economic burdens and others. So you must understand that through engagement in order to make the research feasible.

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Thirdly, we want to make sure that the research that we do is relevant to the population that we are interested in benefiting as well as encourage the uptake and use of the findings. As we have heard, engagement makes the research worthwhile in those aspects. I think that it is truly important, when we are talking about patients who may have a lived experience that is considered rare, that we must truly engage to understand several of these aspects.

I think some of the benefits of this type of model for thinking about research in the setting, are that we actually have an increased knowledge about what we can do that is more effective, but also, patients, their caregivers, and others, feel like they have an increased knowledge, as well as more enthusiasm for the research, even when they may be dealing with these large competing priorities that we have talked about. To build on a point that was mentioned earlier, it will also help improve the trustworthiness of the researchers in the clinical enterprise, which I think is important, when we start to talk about communities that have been historically excluded or marginalized. I think we couldn't have a better understanding of real-world experiences except through the lens of those that have been affected.

Sean Sanders (host):

Thank you all very much for those comments. I just wanted to touch on the use of technology and how it can help. For instance, we have talked about the challenges with patients getting to a clinic to participate in a trial. Telemedicine, that has seen a rise during COVID, seems to be much more accepted now as a way to talk to physicians and clinicians. Any thoughts from the panel on how technologies such as telemedicine and AI might impact how we are thinking about this?

Linda Goler Blount:

I think technology - data science, AI - has great potential. However, we must be careful and cautious. During the height of the COVID epidemic, two years ago, we saw that pulse oximeters didn't work as well on people with dark skin, we saw that Dexamethasone wasn't as effective in African Americans. That wasn't a surprise as when did the research, there were no Black people involved in the trials of that device or that medication. So, I think we must be careful when we think about the role of technology. I happened to co-author a paper a couple of years ago, in which we looked at bias in the machine learning algorithms of the EHR scheduling systems. It turns out that the AI in the scheduling systems was double and triple booking Black patients. There were probably no Black people involved in the development of the machine language or the code, and one wonders who was involved in the testing. So, while this technology was considered an efficiency-producing technology for the optimal operations of a practice, people didn't see that Black patients were being double and triple booked. This means they probably weren't coming back, which has implications for their outcomes: if they are not coming back, if they don't have the time, as it has been said, because they can't take time off work, because of child care issues, transportation, or whatever, if they can't come back and wait for hours, then they may never be seen, which means their conditions may never be addressed. Therefore, I think we need to be careful about putting too much credence into technology. But there is an opportunity to look at what has gone into the technology, what has gone into the machine learning, what has gone into the algorithms and create opportunities to be more inclusive. One of the things we have been talking about are strategic research committees

that work with technology producers as well as obviously hopefully improving the pipeline, so that when the testing occurs, it is inclusive, and we can talk about it being effective for everyone and not just a certain segment of the population.

“But there is an opportunity to look at what has gone into the technology, what has gone into the machine learning, what has gone into the algorithms and create opportunities to be more inclusive.”

Consuelo Wilkins:

I would like to add to Linda's outstanding points. The data that we are using to create algorithms is biased. It is based on these systems of exclusion and exclusionary care practices. We must have people who are doing the research understand what those biases are and think about how to mitigate them. We have still dozens of algorithms that have faulty race corrections and modifiers that, again, are built on racism. We also don't really know what race or ethnicity might be a proxy for. If we accept that these are social constructs, then what are the social and structural factors that we haven't quite captured that those are actually serving as proxies for in these algorithms? Balancing that, do we remove them? But then, we are missing those still key aspects.

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Also, just a word about telehealth and telehealth equity during the pandemic, and trying to think about how we would serve these populations that have been marginalized and minoritized. Telehealth

provided some opportunities, but we were also still trying to force people to use telehealth the way that privileged and resourced people use it. We must learn to be a little more flexible and look at what that looks like, what kinds of apps are required, how much paperwork people have to do before on their tiny device as opposed to people who are having their visits via a computer, which is very different. If you have to go outside to take your visit because you are working in a job where you don't have a desk and a closed door, what does that look like? How is that different? We also all often talk about this digital divide, but many of the populations that we are talking about are very tech savvy. They use their devices for many things in many ways. They just don't use it the way that we think they should or have planned for them to use it around healthcare and research. So, if we would just open our minds to allow them to partner with us so that they can actually design those approaches and strategies, we would probably be a lot more successful.

Jamie Sullivan:

I think we saw some great benefits during the initial period of flexibilities and increased use in telehealth in rare diseases. We also probably missed an opportunity to gather more robust data on how it was being used and how it may or may not have been improving some of the challenges experienced by rare disease patients. But what is the promise of telehealth in rare disease? When we asked patients what some of the most important benefits are, the response was: being able to connect with a specialist out of the state that they live in, especially for those with rural locations or those who have a disease where there is one specialist in one city in the US. Prior to the pandemic, they couldn't connect with that specialist: they have mobility challenges, they are unable to travel or to afford to take three days off work, but maybe they could have taken half of a day off work, or a couple of hours to be in an appointment. Traveling to these centers is just not feasible. Those patients, for the first time, were able to connect with those specialists via telehealth. The policies that were waiving the requirement that an individual must be an established patient of the provider to receive telehealth services and be in the state where that provider is licensed.

Unfortunately, as we have carried on throughout the pandemic, some of those policies have been rolled back. The most potentially beneficial policy to a rare disease patient, that they could see physi-

cians out of state, by and large, has gone away. That flexibility has gone away, and we have reverted to a system of state licensure being required. It is simply not feasible for so many medical providers to go state by state and try to get licensed. That is if the state has allowed their patients to receive care out-of-state regardless of whether they are licensed or not. These policies are impacting everyone, but certainly, for those who are receiving health care benefits through Medicaid, it has even more of an impact. So, we risk losing some of the potential benefit that we have gained over the last couple of years if we don't get our telehealth policies right.

Nakela Cook:

I think some of the comments about the promise of telehealth being very real are informative, but some of the perils that have been emerging, that we are recognizing, really invite us to think about how we understand telehealth more effectively, how we design it, etcetera. I think there is an important research agenda here as well. We have seen in some of the studies that have come out during the pandemic, such as the one by RAND, that actually saw that the increases in the use of telehealth during the pandemic were mostly amongst individuals who are insured, more affluent, and more in metropolitan areas as compared to rural areas. When looking at low-income individuals, in this scenario in California, they found that the telehealth visits were audio only for the majority as opposed to including video. We must understand what those implications are in terms of how different types of telehealth visits affect care outcomes.

I think there is an important research agenda, and some of the data that was coming out from surveying physicians actually highlighted that there were real challenges in implementing this in terms of reimbursement, technology challenges for patients as well as the integration into the electronic health records, especially for individuals that need coordinated care. That is an important component of delivery of this type of service. We need to overcome these types of challenges to see the benefits and for the potential promise of telehealth to come to fruition.

Sean Sanders (host):

Thank you to a fantastic panel, I have learned so much from you and I hope that our audience has as well. Goodbye everyone.



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