The Rare Disease Gazette

Conversations with the world's experts about rare disease

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FUNDING RARE DISEASE RESEARCH

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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 healthcare. 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.

The Rare Disease Gazette is a magazine that broadcasts these discussions.

James Levine

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The Conversation

Experts of the month: Erika Berg, Ph.D, hosts a conversation with world's experts about rare disease: Funding rare disease research: Collaboration to accelerate treatment innovation

The Conversation

Experts of the month

James Levine, Ph.D., M.D., M.B.A.
(Fondation Ipsen, Paris, France)
Adora Ndu, Pharm.D, J.D.
(BridgeBio Pharma, Palo Alto, CA)
Paola Pozzi, M.A.
(Sofinnova Partners, Milan, Italy)
Teri Willey, B.A., M.B.A.
(National Bleeding Disorders Foundation, New York City, USA)

Erika Gebel Berg, Ph.D.
(Science/AAAS, Washington, DC; moderator)

"There is a real groundswell of interest right across this space and there are multiple alternate mechanisms of funding which are becoming more and more interesting. I think venture philanthropy has led the charge in this regard, but you also have social impact bonds, crowdfunding (which is very relevant to patient groups), and collaborative consortia."

– James Levine

Erika Berg (host):
Today we will explore the diverse ecosystem of funders within the rare disease space, including philanthropic organizations, venture philanthropy, impact investors, and biotech developers. We will discuss innovative funding models, the science behind investment efficiency, and the concept of spillover economics. We will also examine how funders can collaborate and how their combined efforts can accelerate research and development (R&D) for rare diseases. I would now like to take the opportunity to welcome a brilliant panel today. I will give each of them a chance to say hello and introduce themselves.

Adora Ndu:
My name is Adora Ndu. I am the Chief Regulatory Affairs Officer and the Executive Vice President of Portfolio Strategy and Management at BridgeBio Pharma. My background is in pharmacy and law, and I have spent the vast majority of my career in regulatory affairs and drug development, with a particular focus on rare diseases, which have really found a near and dear place in my heart and professional life. That is what brought me to BridgeBio. Bridge Bio is a Bay Area biotech company that is focused on developing innovative treatments for rare genetic diseases. We were founded in 2015. Our first two approvals were in 2021 in the ultra-rare disease space. The first was for a disease known as molybdenum cofactor deficiency (MoCD) Type A, which at the time impacted just 400 known patients globally. That was a challenging development program. We worked very closely with the FDA, leveraging things like external controls to get the treatment available for patients. Most recently, we received our third approval in November of 2024 for another rare condition known as transthyretin amyloid (ATTR) cardiomyopathy. We continue to drive forward in spaces that are difficult and challenging based on the science and the biology. We have a number of late-stage programs that are really trying to establish precedent and new therapies for diseases like limb girdle muscular dystrophy, autosomal dominant hypocalcemia type 1 (ADH1) and achondroplasia.

Teri Willey:
My name is Teri Willey. I am the managing director of Pathway to Cures, which is the venture philanthropy fund of the National Bleeding Disorders Foundation. Inheritable bleeding disorders are, by their very nature, rare diseases. So I am working with a small subset of what Adora talked about. We are a venture philanthropy fund, which is very similar to a regular venture fund in that we invest for equity in companies that are developing cures and other solutions to address unmet needs in the inheritable bleeding disorders community. My background has been a combination of venture investing and technology transfer. In general, my vocation has been acting at the interface of for-profit and not-for-profit organizations to ensure that important early-stage life science discoveries are developed for the benefit of the public.

James Levine:
My name is James Levine, and I am President of Fondation Ipsen in Paris. I previously spent three decades at the Mayo Clinic, working in translational research and innovation. I joined Fondation Ipsen several years ago, motivated both by professional experience and personal exposure to rare diseases. At Fondation Ipsen, our work focuses on advancing knowledge, fostering collaboration, and supporting research ecosystems in rare diseases. Through initiatives such as Crossvine Studio, we contribute to academic research, policy analysis, and data-driven approaches aimed at improving the efficiency and sustainability of research investment and accelerating progress toward new treatments.This is an important and evolving discussion, and I am pleased to be part of it.

Paola Pozzi:
I am Paola Pozzi. I am a partner at Sofinnova Partners, which is a leading venture capital firm based in Paris, with offices in London and Milan. We have a clear focus on investing in life sciences. We have seven dedicated strategies that are investing across all the value chains, so starting from early stage to later stage investments. As of today, we manage over €4 billion in assets. I am a partner in one of the early-stage funds, which is dedicated to investing in Italy to create and grow companies that can become global players. There is a specific focus on investing in genetic and rare disorders, thanks to a strategic partnership we established with Fondazione Teleton when we launched the fund in 2018. Fondazione Teleton is a very well-known charity in Italy that has proven to be very successful in supporting basic, translational and clinical research in the rare and genetic space. Many of the programs and products that they have supported have been approved and are now on the market. As of today,

we have invested in 10 companies and we are proud to have a company with clinical-stage programs in inherited retinal disorders, showing good safety data and preliminary evidence of efficacy.

Erika Berg (host):

I would like to put the first question to Teri, but everyone is welcome to add their thoughts. At a high level, what kind of trends are you seeing in research activity, drug development, and clinical approvals for drug developers working in rare diseases?

> ***"We are seeing accelerated growth with rare disease R&D as well as product development in the U.S., but even more so in Europe. There are currently over 10,000 rare diseases, but only about 5% have an FDA-approved therapy, so there is room for new curative therapies and approaches to addressing these unmet needs in the market."***

Teri Willey:

We are seeing accelerated growth with rare disease R&D as well as product development in the U.S., but even more so in Europe. There are currently over 10,000 rare diseases, but only about 5% have an FDA-approved therapy, so there is room for new curative therapies and approaches to addressing these unmet needs in the market. We are also seeing, very importantly, an increase in patient involvement. Patient-centric approaches, including opportunities to do decentralized trials, are so important when you are dealing with small populations so you can meet them where they are to ensure they can participate in these studies. All of that is very important, and we are seeing organizations, like Fondation Ipsen, NORD, Every Life, as well as disease-specific foundations like the National Bleeding Disorders Foundation, that I work for, working together to make sure that government incentives continue to support efforts to address these unmet needs. So there are a lot of good things going on, including an increase in understanding the molecular biology and how these diseases work, which makes a big difference. However, we have to be cognizant of the cost. We have seen some life-changing developments in gene and cellular therapy, but we have also encountered some challenges in addressing payer issues to make sure that these really innovative approaches can continue to change lives.

Adora Ndu:

I would add that, from the regulatory perspective, one of the trends that we are seeing is continued focus on advancing treatments for rare diseases. When you look at the approvals coming out of the Food and Drug Administration (FDA) over the last couple of years, rare diseases have outpaced approvals for novel products. That is promising and our hope is that we continue to see that trend moving in the right direction, because it is so important. Similarly, when you look across the pond to the EU, we continue to see those trends progressing. I know we are going to touch on this, but there is clearly an evolution in the regulatory and legislative environment as well, which is an important trend for drug developers right now. We are trying to navigate this as we try to advance some innovative clinical trial designs and work on aligning with health authorities on drug development, initiating clinical trials, determining the regulatory path forward, and ultimately getting these products approved for patients. So that is another trend that we are navigating.

> ***"With individualized medicine also becoming a mainstream concept, this is probably the most exciting and dynamic time to be in the rare disease space."***

James Levine:

I agree with what has been said. What is particularly striking is the pace of change in the rare disease field. After a period of rapid growth in venture funding, the landscape has clearly recalibrated. At the same time, we are seeing the emergence of new scientific platforms, more adaptive trial designs, and the increasing use of data-driven and computational approaches. Taken together, these developments have the potential to improve how research is conducted and how treatments are developed for conditions where unmet need remains substantial. As more individualized approaches to medicine move into routine practice, rare diseases continue to be an important area for innovation, collaboration, and learning across the wider biomedical ecosystem.

Erika Berg (host):

Paola, can you share with us your take on the current state of public or government funding for rare disease research and therapeutic development relative to other disease areas. What are you seeing?

Paola Pozzi:

I can tell you what Fondazione Teleton has been doing over its 30-year of history in Italy, as an organization solely dedicated to supporting translational research in rare and genetic disorders. They have invested over $740 million, specifically dedicated to translating this research. As I mentioned earlier, they started investing at the preclinical and translational stages, and then they went on to support most of the clinical trials that were then approved by the European Medicines Agency (EMA). For instance, Strimvelis is the first ex vivo gene therapy approved in Europe, and that was in 2016, when the field was still very immature. What Italy has, however, is a strong excellence in advanced therapy development. They work with top scientists that are world-renowned, who, over time, have built not only the basic and translational research capacity, but also all the clinical expertise needed to translate these research programs into products that have been approved and are now available for patients. This charity has been able to do impressive work over the years, through its strong dedication to quality, research, and supporting the best of Italian excellence in this field, and it has really paid off. This results in products that are now available to patients. Strimvelis, for instance, has treated over 45 patients so far. It is indicated for a very rare disease, but the success of this story has also enabled Fondazione Teleton to move more and more products forward. So that is a fascinating story. I am saying this because, before joining Sofinnova Partners and becoming an investor, I spent 14 years in technology transfer in academia. So I have seen this progress firsthand. I was actually in a very prestigious research university hospital at that time where I saw these programs moving from translational work in the lab to the clinic, or the bedside. It has been a really tremendous effort

that turned out to be successful. There are a number of products that are now moving towards approval, while Strimvelis and Lenmeldy, another therapy for metachromatic leukodystrophy (MLD), already have an approval. I think this is only the beginning, but these are success stories that we should highlight and be proud of.

Erika Berg (host):
Any regional differences that we should point out that are different from that experience?

Adora Ndu:
I would add that, historically in the U.S., there have been several mechanisms and tools for federal funding to advance research and development. In the last eight months or so, there has been more uncertainty introduced in that space, especially in terms of funding coming out of the NIH to academic institutions. What I would say is for a company like BridgeBio, when we were founded in 2015, this type of funding was at the core of our ability to identify new compounds. We had a team of, what we called "drug searchers". They were essentially going from institution to institution, meeting with researchers, understanding the science behind novel compounds and the biology of disease, and identifying potential collaborations. So we established a number of collaborations with many academic institutions many years ago. In more recent terms, there have been some disruptions to the funding coming out of NIH, especially to different research institutions. We continue to watch that space to see the progress there and where things land. As far as FDA is concerned, there are a few tools that are available. FDA does issue orphan drug grants, primarily focused on natural history studies. Those are, to my understanding, not impacted to date so we hope that they continue. We also have Advanced Research Projects Agency for Health (ARPA-H) that has their funding programs and the work that they do is very important in the rare disease space. We are hopeful, because a lot of this research is important. It usually feeds into ongoing development that other companies, such as BridgeBio, can then come in and help advance and bring to the finish line. So there is a significant role that federal funding plays. I think we probably have to start to think about novel approaches. Maybe it is more of a public-private approach to funding rare disease drug development. I am sure we will talk about that in detail shortly, but there are certainly regional differences that we should be conscious of.

"We are also encouraged by seeing some foundations step up to address some of the unmet needs in funding because our investments are often in very early-stage companies. Many of them are university or teaching hospital spinouts. So the loss of that type of funding is notable."

Teri Willey:
We are also encouraged by seeing some foundations step up to address some of the unmet needs in funding because our investments are often in very early-stage companies. Many of them are university or teaching hospital spinouts. So the loss of that type of funding is notable. One of our companies recently received an award from Wellcome Leap, from the U.K. Wellcome had put together a £600 million program for addressing unmet needs in certain areas. One of those areas was in bleeding disorders and heavy menstrual bleeding as a real issue and as something that we need to better understand, as an indicator in women's health. So it is exciting to see these types of foundations stepping up, across the world, to focus on areas with unmet needs and to explore how to leverage the good work that is already underway.

James Levine:
I would add a European perspective. At the policy level, rare diseases are recognized as a priority in several European countries, including France, with comparable attention in other Member States. This is reflected at the European level through coordinated initiatives designed to strengthen collaboration, data sharing, and translational capacity across borders. It is important to remember that rare diseases are inherently international, given the small and geographically dispersed patient populations. As a result, international collaboration is not optional but essential. That spirit is reflected in discussions such as this one, where support from public funders, philanthropic organizations, and research agencies across regions contributes to a more connected and resilient research ecosystem. In that context, sustained collaboration between communities—across disciplines, sectors, and geographies—remains a critical enabler of progress.

Erika Berg (host):
Adora, I think you addressed this briefly, but can you talk more about the regulatory environment in this space and how agencies like the FDA or the EMA are incentivizing and prioritizing the development of drugs for rare and orphan diseases?

Adora Ndu:
I will start with the EMA since it is probably more straightforward at the moment. The EMA has always incentivized drug development for rare diseases, and they continue to do so. For example, there are two pathways that I would like to highlight: conditional approval and exceptional circumstances. Both essentially recognize that there will be limitations in the data sets that are submitted for rare disease drug reviews and approvals. These pathways continue to be used, and I think there have been a number of first-in-disease approvals that have gone through them, that have allowed for those treatments to become more broadly available to patients. In the U.S., the FDA, has historically navigated this in a different way and continues to do so. I would say that the FDA is going through a natural evolution, given the change in leadership and the changes in internal structures within the agency. Externally, we are observing and waiting to see where things settle. In general, if we are reading the tea leaves at this time, what we can say is that there is interest and focus in continuing to advance, support and incentivize rare disease drug development. For example, the FDA rolled out the Rare Disease Hub in 2024, which is essentially an infrastructure within the agency aimed to help increase consistency across review divisions and offices, as that was one area of concern that companies were facing. More recently this year we have seen a few things announced. There was a JAMA article, published a couple of months ago, that was penned by the new commissioner of the FDA. One of the things that he talked about was trying to establish this new pathway for rare diseases via a plausible mechanism. So that is something that we will continue to watch. A couple of months ago they also announced this new voucher program, called the Commissioner's National Priority Voucher Program. What that program will do is expedite review and approval. So possibly products could be approved as early as one to two months after the package is submitted, which is pretty significant if we are able to accomplish that, especially as you think about net present value (NPV), funding and return on invest-

ment (ROI). All of these things are directly relevant to this new Commissioner's National Priority Voucher. Now the voucher has not been rolled out specifically for rare diseases, but it does include rare diseases. One of the priorities that have been laid out is addressing a high unmet need. And so, to the extent that these new and innovative products are addressing a high unmet need or represent a significant shift in innovation to treat a particular disease area, they could potentially leverage this voucher to make the treatment available much sooner for patients. More recently, just a matter of days ago, there was a new pathway announced called Rare Disease Evidence Principles, which focuses on very rare diseases, so those affecting less than 1,000 patients. For diseases within that space, a developer would be able to submit an application to FDA. Essentially, what that does is that it allows the agency to collectively recognize that more streamlined, flexible approaches should be applied to this product for this disease. So, for example, this could mean leveraging a single adequate and well-controlled study, plus confirmatory evidence, plus novel biomarkers, and potentially a limited data set to establish the standard of substantial evidence for approval. And so while the packaging of this new incentive that has been rolled out is currently available, my sense is that they are trying to establish a process that makes it easier so that sponsors do not have to receive mixed feedback depending on who is reviewing the product and where it lies. Once you have this designation, you should be able to leverage this. So I think it is a signal saying that they are focused on rare diseases, they are interested, and they are trying to roll out a few incentives for development in this space.

James Levine:
I was struck by something Adora mentioned. In our work in the U.K., including analytical engagement around the MHRA's innovation initiatives in rare diseases, we have looked at how regulatory approaches can influence the broader research and development environment. Beyond supporting individual programs, there appear to be wider system-level effects in terms of attracting activity and encouraging innovation. I would be very interested in your perspective on how important a predictable and enabling regulatory environment is for helping promising therapies progress efficiently toward patients.

"A lot of these rare disease therapies are being developed by very small biotech companies, many of them with only one product under development. It is critical for them to be able to engage with health authorities like MHRA, EMA, and FDA and receive reasonable feedback for pragmatic drug development."

Adora Ndu:
I think it is absolutely critical. The ability for developers to have certainty in the regulatory process, so they can develop their treatments through the most streamlined and efficient drug development pathway possible, and make those treatments available to patients, has tremendous spillover economic benefits. A lot of these rare disease therapies are being developed by very small biotech companies, many of them with only one product under development. It is critical for them to be able to engage with health authorities like MHRA, EMA, and FDA and receive reasonable feedback for pragmatic drug development. That way they can continue to exist and they can actually see their product through to approval, get it to patients, generate revenue, and then continue to expand their development into other areas and other diseases. So it is absolutely critical.

Erika Berg (host):
Let us now talk about some of the funding models that help bring these life-saving medications to market. Teri , to what extent are you seeing dedicated venture capital funding in support of commercial development of new therapies for rare diseases, and how has this activity been changing in recent years?

Teri Willey:
Well, we are very lucky to have Adora's fund among us. Unfortunately, this is not the norm, but it is wonderful to have this type of expertise and smart money in an investment involving a rare disease. What I am seeing are more and more disease-specific foundations enlarging or launching for the first time venture philanthropy funds, and certainly the National Bleeding Disorders Foundation is an example of that. We only launched in 2023, so we are a newcomer in that regard. Part of the contribution to the mission in doing that is to say there are a lot of solutions out there in research laboratories and in early-stage biotech companies. Some of them are specific to our community in bleeding disorders, and some of them are really amazing platforms that could be applied to our patient population. The question is: what would it take for them to move these solutions off the back burner and into their pipeline? What do they need? Oftentimes it is money, but often it involves understanding the patient population. We call them lived-experienced experts. Sometimes it is just about understanding the nuances and the biology of the disease and then having the capability to syndicate, to find other people to co-invest with and establish a strong investment case, in order to bring these ideas to the public and patients in a meaningful way. So we are seeing more disease-specific foundations. We are seeing top-tier and traditional venture funds participate in these rounds, especially when there is a platform involved. In our case, some of our indications might not be their big winner, but they can be very powerful clinical proof of principle, to show that the platform has legs and could lead to impacting the health of even larger populations. That is something that is really exciting. I am starting to see, and this may just be wishful thinking on my part, a continued involvement, and perhaps an increased involvement, from sophisticated family offices across the world that have an interest in rare disease. The challenge is figuring out which ones are interested and doing that kind of matchmaking because there is not a straightforward way to do that. So there is hope in having lots of different varieties of funding along with experienced people, funds and entrepreneurs coming together to put those types of funding rounds together in a way that makes sense, aligns interests, and helps these companies get to the finish line with their product development.

Erika Berg (host):
Paula, you are part of a dedicated program focused on the commercialization of rare disease research from the Telethon Foundation. Can you tell us more about how that program works and how such a design can accelerate the clinical translation for therapies that

are rooted in promising academic research?

> ***"We are an early stage fund, so what we do is pick technologies with breakthrough potential developed in academia and we build companies around them. So we have to be very focused in identifying what we truly believe is a breakthrough therapy with a potential to become a product for rare disease patients."***

Paola Pozzi:
I am going to build on what Teri just said because I am in full agreement with it. We are an early stage fund, so what we do is pick technologies with breakthrough potential developed in academia and we build companies around them. So we have to be very focused in identifying what we truly believe is a breakthrough therapy with a potential to become a product for rare disease patients. It is quite difficult, because we have to invest early and when we invest, we typically invest at the seed stage. This can be from a couple of million up to four million, for a seed investment. We have to make sure that these seed investments can grow the company and attract dedicated funding, so that the programs actually reach clinical proof of concept. So that is really the challenge for us, as a venture fund focused on early-stage investments: being able to select opportunities based on quality and what we believe is the best science available, while making sure that what has been done and promoted at the academic level can be translated into entrepreneurial and industry settings.

It is a long journey, and I am saying this because I am mostly focused on investing in advanced therapies because, as I mentioned, Italy has a renowned excellence in this field. We therefore know that these are highly capital intensive investments. So, when we decide to make an investment, we set a high bar. At Sofinnova, we always say that we invest not only in science but in the right team. The team behind the project is crucial, so the early developers in academia, but also being able to develop the right team that is successfully translating to the clinic. I am talking about the regulators and managing all the CMC (Chemistry, Manufacturing, and Controls) efforts behind the programs that need to be further supported, and having the right managerial experience to bring these companies forward and ensure successful clinical translation.

Erika Berg (host):
James, we talked about how rare disease research can produce spillover benefits in terms of those beyond the direct benefit to any one patient community in domains such as technology development or biological knowledge. Can you talk about these effects and how they can amplify the impact of an R&D investment in rare disease research?

James Levine:
I think there has been an evolution in how we understand spillover effects in rare disease research. Early on, spillovers were often discussed primarily in market terms—whether insights from a rare condition might later be applied to more common diseases. While that remains relevant, the concept has matured and broadened. Today, spillovers are increasingly associated with shared platforms, methodologies, and infrastructures, such as enabling technologies, data generation, and approaches to evidence development that can be applied across multiple rare diseases. In this sense, spillover value is not only about market expansion, but also about improving access, reducing development costs, and accelerating timelines. Importantly, spillovers are no longer purely economic. Advances in areas such as data science and computational methods have the potential to support more efficient therapeutic development across diverse disease areas. As these approaches continue to evolve, they may play an important role in shaping more sustainable and responsive therapeutic ecosystems.

Adora Ndu:
I could not agree more. When I think about development and the regulatory space, quite often the spillover is certainly there. It is what we saw in the field of oncology, with a lot of innovative approaches within the oncology space. Similar conversations are now happening when we look at rare diseases and what we can take from rare diseases and apply to more common diseases with regards to some of the trial designs, development of novel biomarkers, use of a single adequate and well-controlled study and what level of data should be sufficient, and the role of confirmatory evidence in those instances. So we are certainly seeing that and the ultimate impact of that is it streamlines drug development. It reduces costs of drug development. It reduces the time of the end-to-end cycle of development from the non-clinical to clinical and, ultimately, to commercialization.

James Levine:
I would add that improving the efficiency of therapeutic development has the potential to influence affordability over time. Cost remains a significant barrier to access in many health systems, and this is particularly relevant in areas of high unmet need. For that reason, discussions about investment incentives, efficiency, and sustainability are not abstract; they are closely linked to questions of access and long-term impact. These are important considerations as the field continues to evolve.

Erika Berg (host):
Teri, as an investor, what are some of the key considerations that you look for when bringing a potentially promising rare disease startup into your portfolio?

Teri Willey:
The considerations are traditional venture considerations for the most part. We invest like a traditional early-stage life sciences investor in many ways. We want to make sure that the idea is solid and the team is solid or we can attract the team to the company. I think the way that we differ is that we are narrowly focused on inheritable blood and bleeding disorders. We do not have a traditional venture structure, in that we do not have traditional limited partners that we share returns with. We are an evergreen fund and our funding comes from donors. So any equity realizations or returns on our investment go back into the fund for reinvestment and to support our community. That is one way in which we are different. In order for the companies we invest in to be successful, they must have a strong investment case for traditional investors, and follow that best practice. I think that is very important. The way that this fund is different than the other types of investing I have worked in is that we put a very heavy emphasis on the front end, so on science and clinical evaluation. We have an amazing scientific advisory group made up of key opinion leaders, mostly from the U.S., but also

from around the world, in the field of inheritable blood and bleeding disorders. They are available to us as volunteers. We meet at least monthly, and usually more often, to review specific opportunities. This is proving to be extraordinary in terms of the insights we can gain and the advice we can give back to the companies as well, because we want them all to be successful, whether we invest in them or not. Then we move on to our traditional investment committee and the development of an investment memo and investment case. So even though we are a venture philanthropy, we are only successful if we can build the strong investment case that attracts syndicate partners.

"I think that being aligned with the needs of patients is the most powerful funding mechanism imaginable."

James Levine:
Teri, I think you have highlighted an important point: venture philanthropy should be understood as a complementary, and often highly effective, approach to supporting therapeutic development. In disease-focused settings, it brings deep domain expertise and sustained engagement with patient communities, which can be especially valuable in shaping research priorities and development strategies. Alignment with patient needs is a defining strength of this model, and patient perspectives are increasingly recognized by regulators as an important part of the development process. In that sense, venture philanthropy has demonstrated how mission-driven investment can play a meaningful role alongside more traditional funding approaches in advancing treatments for rare diseases.

Erika Berg (host):
Are there any other important ways in which venture philanthropy differs from traditional approaches to venture capital and other venture funding models?

"What you see is that venture philanthropists are less worried about an early stage molecule or biologic not making it. They are much more committed to whether this has the potential to impact the patients receiving cures. It is that strong commitment to patients that I think is what differentiates venture philanthropy from true venture capitalism."

James Levine:
One of the distinguishing features of venture philanthropy is the centrality of patient impact in decision-making. In disease-focused philanthropic models, investment choices are often guided as much by potential benefit to patients as by traditional measures of technical or financial risk.

Experience across multiple initiatives suggests that this orientation can support a different, but not necessarily riskier, approach to early-stage development; one that prioritizes long-term impact and sustained engagement over short-term outcomes. As the governance and professionalization of venture philanthropy have continued to mature, it has emerged as a credible and complementary mechanism within the broader innovation and funding ecosystem for rare diseases.

Teri Willey:
One of the common themes that emerged as we were looking at our pipeline of companies, having met with about 220 companies since we launched, which is a small number compared to the throughput in traditional venture funds, was that they were late in engaging patients. We saw this particularly with companies that were already into the clinic or getting ready to launch their first human studies. Because of that, there were certain nuances in the study design that could have been corrected earlier. What I mean by that is they had put together solid clinical models and study designs sufficient to get them approved by the FDA, but with a product that was not going to be as attractive to the people that they were trying to reach. So they might have an FDA-approved product, but maybe not one that would achieve the market penetration that they hoped for, to put it in business terms. So one of the things that has been very important to us is to continue to engage patients earlier and earlier. Even when we are not investing, we advise companies by putting our virtual advisor groups together with patients to ensure they are considering these nuances because they are critical to their success. This approach is highly synergistic, helping companies reach patients more efficiently and sooner.

Paola Pozzi:
I fully agree with what Teri just said. We are seeing the same in our portfolio company. Engaging with patient advocacy groups and patient associations earlier, and recognizing the benefits of doing so, is vital to successfully translating these products to the clinic.

"Because when you speak with companies, it is fascinating how many drugs for very rare diseases are shelved. They are sitting on shelves across many companies and academic institutions, primarily because of funding. So the mechanism to take these products off the shelf, including bringing together funding, with venture philanthropy being one of the key areas for advancing these treatments, represents a huge opportunity. I think these conversations need to continue so that the products that were shelved, not due to a lack of solid science but due to a lack of commercial viability and therefore inadequate funding, can be taken off the shelves and put into the hands of patients."

Adora Ndu:
I would agree that in both the for-profit as well as the non-profit model it is critical. At BridgeBio, the patient voice is at the core of every decision we make, even as a for-profit company. It is critical at early, middle, and late stages. So when we are doing some exploratory work to identify different conditions that we would like to pursue in research and development, we

are speaking with the patient community. When we are developing the protocols, we are speaking with the patient community. When we are engaging with regulators, we are speaking and involving the patient community throughout that process. One thing I wanted to build on with regards to the venture philanthropy discussion was that I think that this is critical, especially in the ultra-rare disease space. These are the diseases where the commercial viability is limited or nonexistent. So for the products that are either NPV neutral or marginally positive, thinking about the innovative funding models that could enable products that have solid science to continue to advance is important. There is a sort of groundswell happening right now, with different groups looking at this very carefully. We have been involved in a number of conversations to explore what can be done to help enable this conversation and create some actual traction. Because when you speak with companies, it is fascinating how many drugs for very rare diseases are shelved. They are sitting on shelves across many companies and academic institutions, primarily because of funding. So the mechanism to take these products off the shelf, including bringing together funding, with venture philanthropy being one of the key areas for advancing these treatments, represents a huge opportunity. I think these conversations need to continue so that the products that were shelved, not due to a lack of solid science but due to a lack of commercial viability and therefore inadequate funding, can be taken off the shelves and put into the hands of patients.

"There is a real groundswell of interest right across this space and there are multiple alternate mechanisms of funding which are becoming more and more interesting. I think venture philanthropy has led the charge in this regard, but you also have social impact bonds, crowdfunding (which is very relevant to patient groups), and collaborative consortia."

James Levine:
I agree. One area of interest for us has been the idea of aggregating or coordinating assets and initiatives, with the aim of creating more sustainable development pathways across multiple rare diseases. Rather than focusing on single programs in isolation, this kind of approach can help align resources, expertise, and incentives in a way that supports broader patient communities. We are also seeing growing interest in a range of complementary funding mechanisms, including venture philanthropy, collaborative consortia, and other mission-driven or policy-enabled models. Taken together, these approaches reflect a wider effort to place patients more centrally within research and investment decisions. In that context, rare diseases continue to serve as an important testbed for more individualized, patient-focused approaches to innovation, with lessons that may inform the wider health ecosystem over time.

Erika Berg (host):
Paula, given the small number of patients for a particular medication, what are some strategies that make taking on such a risk more compelling to investors?

"We have to build investment cases that are strong, while making sure that we have all the enabling elements in place to make these products affordable to patients."

Paola Pozzi:
I think we need to make sure that we are implementing efficiently and optimizing all different strategies. We have been talking about philanthropy and venture capital investments. We have to build investment cases that are strong, while making sure that we have all the enabling elements in place to make these products affordable to patients. It is a really long cycle, but we have to make sure that all the key players are working together to make these products available to patients in an efficient way. I am also thinking about the fragmentation that there is in this environment. We need to work together to avoid fragmentation, for example, at the regulatory level, while also streamlining operations and improving efficiency in clinical translation, so including all the expedited pathways that were mentioned earlier. Importantly, we also need to consider the cost of goods for these therapies, especially in advanced therapies, as they heavily affect their adoption by patients.

"Above all it comes down to quality, capacity, and capital efficiency. As investors, we have to ensure that the product being delivered at the end of the day becomes sustainable for the health system."

I believe it is a combination of factors, but above all we have to make sure that we are investing in high quality and that we are supporting the translational research moving forward. I would also like to mention the importance of improving the diagnosis of these patients, because there are so many undiagnosed patients out there. If we are able to improve the diagnosis, by using artificial intelligence that James mentioned earlier, we can increase the number of patients that can actually benefit from these therapies. What I am saying is that there are a number of factors that we need to align to make sure that we are streamlining the approval process for these therapies. Above all it comes down to quality, capacity, and capital efficiency. As investors, we have to ensure that the product being delivered at the end of the day becomes sustainable for the health system.

"The economic consequence is straightforward: if you can better de-risk, investments are more efficient, which brings more investors to the table, and ultimately you can have cures much more quickly through simple financial structures. "

James Levine:
I agree. One important point that is sometimes left implicit is the role of risk itself in shaping outcomes in rare disease development. As in many areas of biomedical research, attrition rates are high, and this makes efficiency and risk management particularly important considerations.

There is growing recognition that improving how risk is assessed and managed, through better data, more robust early evaluation, and coordinated approaches, can help make research and development pathways more sustainable. In that sense, de-risking is not about eliminating uncertainty, but about making more informed decisions earlier. Ongoing work across the field, including collaborative analyses and shared methodologies, suggests that advances in data availability and analytical tools may further support these efforts over time, with potential benefits for both investors and, ultimately, patients.

Adora Ndu:
I completely agree. To build on what has already been said, starting with solid science is foundational. The compound must be strong from a safety and efficacy perspective and demonstrating proof of concept through the clinic is critical. I think that is foundational for any product development and for being able to take that forward and ensure that you have the ROI. I also want to expand on the efficiency piece. Efficiency is crucial in two areas: operationally and in research and development. Efficient research and development really looks like pragmatic drug design, expedited clinical trial recruitment, being able to initiate your trials very quickly, and being able to think through innovative approaches to actually speed up the drug development. That requires a little bit of foresight and rigorous negotiation with the agency to really align on what is essentially the basic requirement or the minimum data set that is required in order for us to understand and have confidence that this treatment is safe and effective so that we can advance that forward. On the operational side, efficiency is one of the areas, in addition to science and patient engagement, that BridgeBio has worked on to optimize.

That is, at the core, another foundational pillar of our organization because we are a hub and spoke model. We have our central organization, our central services, which is where we have a few of the shared services. Then we have smaller companies that we have spun out. Each of those companies is focused on driving and executing the development of specific program areas. They are lean teams, they are experts, and they are focused on executing. This structure allows us to spread risk across the organization because each of these companies is focused on distinct disease areas. We are able to pull in experts within each of these smaller companies and the benefit is that if one product does not make it to a certain milestone, it does not impact the rest of the portfolio and the rest of the organization. So from a de-risking perspective, that is also one of the core areas that we are focused on. We actually published an article in 2024 in the Journal of Portfolio Management where we talk about the model that BridgeBio has leveraged and established to move very quickly and minimize risk, with a very lean operating infrastructure.

Erika Berg (host):
Are there other innovative funding models that you see emerging that could meaningfully move the needle in terms of accelerating rare disease drug development? I would love it if everyone took a turn sharing their thoughts.

> ***"Finally, we need to avoid the fragmentation among the different systems, because at the end of the day, we are all doing this work for the benefit of patients."***

Paola Pozzi:
The funding model itself needs to look at return on investment and building a really strong investment case. What I liked about the conversation today is how we also highlighted the importance of leveraging, for example with platform technologies, so taking the lessons from one product and applying them to another and making this process more efficient. What I would very much encourage is platform-expedited designation programs that are more and more facilitated and put into practice. I would also like to see other models that are also efficiently sustaining and helping companies to be capital efficient. The priority revenue voucher, for example, is a great benefit to whoever is developing these kinds of drugs. I think that what we have to make sure of is that we combine and have access to different funding opportunities. It is not venture capital alone that can solve the problem. It is a combination of factors and it is essential to have a streamlined regulatory framework that really enables this efficiently. Finally, we need to avoid the fragmentation among the different systems, because at the end of the day, we are all doing this work for the benefit of patients. So, it does not really matter who is doing it. As long as we are maintaining the quality and making this an efficient process, it should work out.

James Levine:
It does feel as though several important developments are coming together in the rare disease space. Advances in scientific platforms, data-driven approaches, evolving regulatory frameworks, and more thoughtful approaches to risk are all influencing how research and development is carried out. Taken together, these trends suggest a moment of meaningful opportunity for the field, and forums like this are valuable for examining how they can be aligned responsibly to support progress for patients.

Teri Willey:
At the end of the day, it still takes people to coordinate all of this, to line it up, and make sure that all the smart people play nice together so we can make this happen. I think that is very important. One group that we are grateful to is LaunchBio, for doing that kind of matchmaking between rare disease startups and investors and now, more increasingly with family offices as well. Despite all of the new technologies and innovations that we have, it still takes people to pull it all together and make it happen.

> ***"We see a lot of families that are really searching for treatment for their disease or their child's disease. You even see families and parents becoming drug developers because nobody else is doing anything in that space. As a result, there are many small companies that have been established by families. I think there is an opportunity to think about how to enable research in that space, where no research is currently happening. Establishing a federal fund dedicated to ultra- rare diseases, where there is no commercial viability, could help advance these forward."***

Adora Ndu:
Paola, I heard you mention the priority review voucher, which I think is a critical and a much appreciated incentive for drug development in the pediatric rare disease space. As we all know, it was not reauthorized. We are waiting very patiently to see if it will be reauthorized because that voucher has proven to be a lifeline for many developers that are in the rare disease space. For our first approval, we received the priority review voucher, we sold it, and we were able to redistribute the revenue across other development areas to continue drug development in this space. So it is critical. The second point that I would add on the wish list, is the role that a federal fund could play in the ultra-rare disease space, where no commercial development exists. We see a lot of families that are really searching for treatment for their disease or their child's disease. You even see families and parents becoming drug developers because nobody else is doing anything in that space. As a result, there are many small companies that have been established by families. I think there is an opportunity to think about how to enable research in that space, where no research is currently happening. Establishing a federal fund dedicated to ultra- rare diseases, where there is no commercial viability, could help advance these forward.

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