FROM RISK TO REWARD: ADVANCING DRUG DEVELOPMENT FOR RARE DISEASE

Caitlyn Barrett 00:09

Good morning, everyone. It is so nice to see so many smiling faces. First session of the Future of Health Summit. Very, very exciting. I am Caitlyn Barrett, and I'm a member of the Science Philanthropy Accelerator at the Milken Institute, and it is an honor to be here with you all. Prior to starting with my introductions of the individuals on stage, I have a little audience participation. I usually hate it, but today we're going to go with it. Can you please raise your hand if you have a rare disease, know someone with a rare disease, have a close family member or friend? Raise hands. I think everyone on this stage can raise their hands as well. Perfect. Perfect. Thank you so much. So because of that, how many of you know way more than you should about the health-care system? Yeah, because you have to deal with it. You are your best advocates. So, we are here to discuss one of the most challenging and inspiring frontiers in biomedical innovation: developing therapies for rare diseases. With thousands of rare diseases affecting millions worldwide, the challenges are steep: small patient populations, fragmented data, limited funding, and complex regulatory pathways. But it's not all bad news—because of the people on this stage, because of the people in this audience, rare disease research has reached a tipping point, with the confluence of scientific and technological developments that, if appropriately harnessed, could lead to key breakthroughs and treatments. This panel brings together people who are at the leading edge of necessary change, leaders who are building alliances, rethinking funding, reshaping regulation, and proving collaboration and innovation can accelerate true impact. Very briefly, I will do introductions to each of the people on stage. We have first Terry Jo Bichell, she is the CEO of COMBINEDBrain, a neuroscientist, and a parent advocate who built a precompetitive alliance model that unites patient groups, researchers, and industry around shared data and research goals. We also have Rachel Butler, the president of the Catalytic Impact Foundation. She leads an evergreen fund model designed to sustain mission driven investments in high-risk, high-impact biomedical innovation. Then we have Giacomo Chiesi. He's the head of global rare diseases for the Chiesi Group. He oversees a global portfolio advancing rare disease therapeutics with a focus on partnership, sustainability, and innovation. Really critical pieces of the discussion we'll have today. Then Adora Ndu, she is the chief regulatory officer and executive vice president, portfolio strategy and

management at Bridgebio Pharma. She combines regulatory expertise and strategic insight to align innovation, patient access, and affordability, and rare disease development. And then, finally, last but not least, Marshall Summar. He is the CEO of Uncommon Cures, a pioneer in system level change for rare disease care, and thought leader on policy infrastructure and sustainable delivery models. Those are brief overviews of what they do, but they don't really give you the essence of what they do. So, very quickly, I'm going to ask that each of you share a little bit more about the focus of your work and a mechanism that's been particularly successful in driving your efforts in the rare disease space. So Terry Jo, can we start with you?

Terry Jo Bichell 04:04

Sure. So I am the parent of a 26 year old with Angelman syndrome. He was diagnosed when he was 16 months old. He is now in a lifechanging disease-altering clinical trial. It took 22 years to get there. We did not want that to happen to anybody else, so we formed COMBINEDBrain based on everything we learned from the Angelman field, so that we could shorten that time frame. From 22 years, hopefully down to eight years, five years, three years, one year—and help all these other disorders—120 of them—who are part of COMBINEDBrain get from diagnosis to the FDA as fast as possible.

Caitlyn Barrett 04:56

Yeah, I think that's really critical. I think using a model that you already had established and leveraging it to expand and scale is a really critical piece of what you do. Thank you so much. Rachel.

Rachel Butler 05:10

Yes, well, thank you for having me. I'm the president of the Catalytic Impact Foundation, and we were really launched as an organization to bring solutions to early funding of difficult areas of health care, and there really is no more difficult area than rare disease. But, so we are a not-for-profit 501(c)(3) we take philanthropic capital and we pool it, and then it's permanent self-regenerating capital. We invest in companies, we don't give grants. When those companies are successful, the returns go right back into the fund to be redeployed, to fund other innovative young companies that, for whatever reason, may not yet be ready or attractive to a more traditional source of funding, such as venture capital. So, we focus on children's health, rare disease, women's health, brain and mental health, among other areas, but each of those are areas where it is harder to get funding, and they are, you know—for different reasons. And could be small patient populations could be, you know, an area where there have been a lot of failures. So to the outside world, we look like venture capital, except we can go in earlier. We can take a longer time frame, because we are not sort of beholden to limited partners expecting certain levels of return, but we do want return. We're doing equity investments because we want to build the fund and be able to fund more worthy companies.

Caitlyn Barrett 06:52

I think the evergreen model is one that we'll have to come back to because when you address unmet need and funding, it's hard to keep that evergreen, so I'm really excited to talk to you more about that. Giacomo, please tell us a little bit about yourself.

Giacomo Chiesi 07:09

Of course, first of all, thanks for being for being here all of you, and thanks for having me, appreciate Caitlyn. Chiesi is a family business. We've been around for 90 years. Company was funded by my anonymous grandfather in 1935. We've been, for the longest time, in neonatology, as well as pulmonary diseases, and six years ago, we decided to start our adventure in rare diseases. The reason we did it is primarily because we see ourselves as a family for families, as a family that wants to have an impact, a positive one, and transform people's lives. When we started rare diseases six years ago, we didn't necessarily know what was going to be of it, but in six years, we've now created an organization that has 800 people. We have 10 commercial stage therapies. We're present in 32 different countries, and we have about 13,000 patients currently on our therapies, either commercially or through compassionate use or expanded access or individual funding requests. We also have a nascent pipeline of therapies that are based on gene therapy or complex enzymes that can potentially cross the thrombin barrier. I think the two things that have distinguished us and that continue to be central to what we do are, number one, the unwavering commitment to patients and the fact that we know we have an obligation. We feel that obligation to leave this place a better one than what we have found when the company was set up in 1935. And then the second one is having a holistic view, knowing that patients know no boundaries, they have no nationality. And therefore, once you bring something to patients, you should be able to bring it to all the patients at a global level, in every single country. That's who we are in a nutshell.

Caitlyn Barrett 09:04

Wonderful. Thank you so much. I think, in including kind of this global theme, we will all address some equity issues as well. And because rare disease does, it crosses so many different areas, and a lot of the rare disease therapeutics that we're coming up with are expensive; expensive to develop, expensive to deploy. I think a lot of you are getting creative about how we do that, but I think that some of the conversation can drift in that direction as well. Adora.

Adora Ndu 09:36

Adora Ndu. I am the chief regulatory officer with BridgeBio Pharma. And BridgeBio is quite unique in our story and our history. We were founded in 2015 so about 10 years ago, and our focus has been on developing innovative treatments for genetic diseases, primarily rare diseases. And over this short period of time, our model, which leverages a portfolio model, which we'll talk about a little bit more, has been able to advance three approved products over 19 INDs. Within our history, we've had five positive phase three trials. That's 100 percent of all of our phase three trials have been positive, and a big part of that is

multifaceted. It includes our focus on scientific rigor, how we select our assets. We pride ourselves in having a pretty sharp group of drug hunters. Our focus on patients first. It'll, you know, possibly surprise you that every single decision that we make from the top down, we come back to what's the best thing for our patient community. Whether it's, you know, the endpoints that we're selecting our trial design, or whether we're the best ones to commercialize a product. We're really thinking about, how do we get these treatments into the hands of patients as quickly as possible. And then also we think through how to spread risk, how to minimize risk, both from a development perspective as well as financially. And ultimately, we hope to, and we aspire to, get treatments in the hands of patients as quickly as possible. So when we think about our trial designs, the biomarkers that we select, and our approaches to regulatory flexibility and those engagements, not just with patient organizations, but other stakeholders, including regulators, a big part of our calculus is, how do we get these these treatments, in the hands of of those who need it the most, and how do we get it accessible as well. That's also an important element of what we hope to do.

Caitlyn Barrett 11:45

Absolutely, I'm so glad you mentioned endpoints and biomarkers. I think everyone on this stage has been thinking about those quite a bit, and I know you're the expert in that space, but in a rare disease, being able to find the right ones at the right time for the right purpose are really—it's really difficult. So we can delve into that more as well. And finally, we have, Marshall. Please share a little bit about yourself.

Marshall Summar 12:11

So my journey in rare disease began about 1985 so I trained as a clinical and biochemical geneticist, spent 25 years in the clinical faculty at Vanderbilt then moved to Children's National when, after we finished up the Human Genome Project, we realized rare disease was actually becoming a unique field by itself. So we built out a Rare Disease Institute. There is a clinical home truly for rare diseases along the way, one of the things I discovered I was part of somewhere north of 150 different clinical trials across those 40 years. And what I can say is we were always trying to fit a round peg in a square hole. The university system is not well designed for being speedy. It's not supposed to be. But also, too, a lot of the things that we were bringing to clinical trials really were fit for much larger studies, and not well designed for rare disease. So working with Janet Woodcock, Andrew Lowe, and Simon Frost and others—we kind of came up with this concept of, what if we popped it out? What if we took the folks from the academic world and actually set up a model where we can flip contracts in four or five days, where we can do IRBs using commercial IRB and actually create a centralized site so there's much more predictability, and so that our experiments been running for about two and a half years. And what we're finding is you can actually compress time. You can actually get a little bit better quality on the data with the same team doing it all the time. As a division chief, I was turning down half to two thirds of the studies people brought with us because anyone who's been around the rare disease clinical world knows that the wait times are horrible. They're sometimes up to a year. And so to actually bring a trial into your program means that you've got to pull someone out of clinic to do that. So we tried to create sort of a purpose built model for that. It's been one of the most interesting things I have ever done in my career.

Caitlyn Barrett 14:06

I think structural changes. Thinking about how we pursue a field that has been ignored for a long time and systems have built up under other spaces is really, really critical aspect of what you do, Marshall, I think.

Marshall Summar 14:25

And whether it's regulators or whether it's industry, take your vote. They've sort of got a mindset of "this is how we've done it for the last number of years." And then rare disease is just different. You really do have to take a different look at it.

Caitlyn Barrett 14:36

Absolutely. In my rush to get us started in the conversation I completely forgot. You will probably see popping up on the screen a QR code. There it is. Oh, great job back there. Thank you. If you do have questions, I will try and integrate them into the discussion. I will have a little extra time at the end. So please feel free to submit them. Okay, so one of the things I think we're going to hear a lot about today is community and collaboration, and I think one of the things that I'd like to do to start off is look at kind of a concrete example of collaboration and where it has been meaningfully applied and we can see kind of this is our foundation for the discussion. So what I'd like to do is start with Terry Jo. Can you share a case study of a disease community that advanced through COMBINEDBrains collaboration, and what lessons came out of that case?

Terry Jo Bichell 15:43

I think I'll talk about GABA receptor group. I could talk about 20 different, 30 different groups, but this one has already advanced to treatment in a very short period of time. The GABA receptor community had never formed a foundation. There was no nonprofit to represent them, and they—we helped them form their nonprofit, gave them some of the expertise in that so they could become an entity. And then we work on a precompetitive model, so we pool resources for all these little bitty groups from, you know, the very beginning, so that they can have all the resources they need. A biorepository. They can collect biosamples. They can collect data from day one for free once they join COMBINEDBrain. We list—we have industry partners, and we listen to our industry partners. They tell us what they need. They need biomarkers, they need more data, they need EEGs. So we have all these resources, and some of our little groups take full advantage of all that we have to offer. And this GABA receptor group did that. So they started collecting data immediately, we were able to advise them on the right data to collect, the way to do it, the endpoints that they needed to look at. We have a stable of neuroscientists called the Brain Trust, and we provide sort of scientific consulting to these little groups so that they can get ideas for what directions they need to go, what gaps they need to fill. So this group—the CURE GABA-A Variants Group—they took advantage of all of that, collected blood, made IPSCs, stem cells out of that blood, collected data,

got EEGs, designed the clinical trial. Working with a company called Grann Therapeutics, the first child has already advanced through phase one, phase two trials, and it's a safe lipid nanoparticle delivery system. And we'll see in the future whether there's also efficacy. But that's a pretty good case study.

Caitlyn Barrett 18:22

I'd say it's inspirational, absolutely. So I want to pick up on something that you mentioned, and it was at the very beginning, and it was this: There was no organization around this disease, and I assume that our friends in industry face some challenges when that is the case—how do you find the people? How do you find the data? What are you thinking about there? So I'd love to start with Giacomo and kind of get your take on what it looks like to work with patient organizations and patients individually, and how they can be really successful working with you. Do they need Terry Jo first?

Giacomo Chiesi 19:03

Well, honestly, in a lot of cases, yes, that's our experience. So working with patient advocacy groups requires a specialized skill set on the part of a company; at least that's true of our experience. The first aspect in these situations is that you don't have an adequate knowledge of the disease, if the disease is ultra rare, and perhaps there is, for example, no natural history study, or there is a limited literature that explains what the pathophysiology of the disease is, or what the potential mechanisms of action could be that could represent potential targets for a candidate in a pharmacological drug development type of conversation. So the first thing that you need to do is enabling individual patients or families with tools—potentially also with funding—to set up their own patient advocacy groups. And—for example, our head of patient advocacy, Stuart Seidman—who had a son who had one of the mucopolysaccharidoses—that's exactly what he did, and that's essentially where a lot of his experience comes from. Building tools, building means, building advocacy, building understanding of the disease where there is nothing. So, as a company, whatever you can do to support the patient advocacy groups in their nascent moments, with funding, with tools, with everything, with network, even with knowledge, it's going to make a difference for those. The first thing that's needed in those cases is a long-term perspective—understanding that not every single thing that you do, not every minute you dedicate to this, is going to have an immediate payoff. Right? It's going to come back. It's worth doing it, but you don't need to seek that financial return out of the bat as a company. So you need to be a little different from a DNA perspective.

Marshall Summar 21:00

Can I add something on top of that? Because I think you hit a really important point. It's going to be a long-term relationship with the patient community. It's going to be much deeper than your typical industry interaction with the patient community. Sixty pecent of rare disease clinical trials that fail, fail because of recruitment retention, and so not only is it the right thing to do, it's also going to give you a higher chance of success by engaging with the patient communities early, and the patient communities engaging with the potential industry partners so they know each other. It's—you're not parachuting in, so to speak. And I think that you're really going to have a much stronger program when you do that.

Adora Ndu 21:40

Yeah, I couldn't agree more. I mean, you know, in our experience, what we see is that there are many different types and flavors of patient groups, just given how rare many of these diseases are, and sometimes there is no patient organization. So we have to also think through that. You know, some patient groups are doing a lot of social coordinating. Some are larger, some are, you know, more established and have been around for a long time. And there's a place for each of them to really have a voice and be able to contribute and drive how we're thinking about drug development in the space. And as a company, you know, we come in with our—with authenticity, with an openness to learn and understand. It really informs how we think about, you know, what's meaningful to the patients? You know, what outcomes are important, how we design our trials? You know, Giacomo mentioned the endpoints, etc. And also extending from beginning to end. We have to think about our patient engagement end to end, and thinking about, you know, from the umbrella organizations to the disease specific organizations, and ensuring that we are attentive and we are incorporating. There's nothing like, you know, listening and not using the information. So we also have to be very thoughtful in how we incorporate the learnings that we're gathering from patient organizations and pulling them or collaborating with them along the way. And so when I think about, for example, my specific space, which usually ends up being on the regulatory side, ensuring transparency into how those discussions are going, including patients and patient groups in our meetings. We do that quite frequently. It's good to be able to hear, it's good for them to be able to give us their perspective after sitting through those types of meetings. And I would say for the regulators, that's an opportunity for them to hear directly from patients and patient groups, so that they can contextualize what they are seeing beyond the four corners of a review document. And that tends to be really important in rare diseases, where, when you look at changes and the data, being able to hear how patients are actually impacted can be important in the decision making there as well.

Marshall Summar 24:05

There's kind of been a pivot the last 10 years too. It used to be pull, but industry would go and find the patient groups and say, we want to work with you. What I've been seeing more and more is I think the patient groups got tired of waiting for the train to get here. And so they're actually going out and developing the research, developing the products, getting things ready, and then they're going out and sort of picking who they want to work with in industry from that. And I think we're going to see that model more and more, particularly as the number of rare diseases climbs.

Rachel Butler 24:37

Yeah, I would just add from also from a funding perspective—I mean, these families, especially families of children with rare diseases, are a very, very powerful troop. Nothing is more—has more power than a mom on a mission. And so we see, you know, there are so many small foundations that are started either in memory of a child who has died from a rare disease or working to find cures for a child who's living with a rare disease. We, you know—they raise money, they fund basic research, they hunt down, as you were saying—they hunt down scientists top. You know, say you're working on something that could be

applicable to my child's disease. They start drug companies. They—I mean, it's really remarkable, and they're having effect. And, I mean, there are examples, some somewhat famous ones, of people who have cured themselves by just, you know, diving in and researching when there was nothing else available for them, and finding no repurposed drug that or an existing drug that could be potentially helpful. So, you know, but from a funding perspective, they raise a lot of money, they have strong voices, they are incredibly proactive in funding and searching out who they want to work with. So it's really remarkable. I don't think that exists really in any other area of medicine.

Adora Ndu 26:06

Yeah and I would add that it's so important to have that. I mean, when we think about the over 10,000 diseases, and we have parents, as you've mentioned, that are starting up companies that are doing the drug development that raising funding, we absolutely need that. We absolutely need that. So it's making a big impact.

Marshall Summar 26:25

And for those of you in the audience who are in industry, and if you're going to be working with a patient advocacy organization, it will be different from any relationship you've had. They are going to push you, they are going to hold you accountable. It's not going to be a passive relationship where, oh great another statin. Now they say, okay, well, how are we moving this forward, and how are we doing it quickly? Because for these families, that is actually—the clock is ticking.

Terry Jo Bichell 26:51

Well,and also—I mean I see in the room some of the leaders of our member organizations, and these organizations also educate all of the families that are part of their organizations. And so they are the doorway to finding patients. They're the doorway to getting all of the samples, the biomarkers, the data, everything else. And then, when it's time for a clinical trial, they push, they have already worked with all the families, so the families know why it's important, how to be part of it, what to do, what's expected of them. So the groups that are part of COMBINEDBrain, they are really pushing the envelope, and they are partners with the industry members that are there.

Caitlyn Barrett 27:39

This is a lot of responsibility for patients to hold and families to hold. And so because each of you on this stage are trying to lower the activation energy and reduce some of that stress on them, I'd like to kind of pursue that avenue now. And Rachel, I'd love to start with you, because we heard from Giacomo that there may not be returns you have to really balance and be thoughtful about your portfolio, and so I'd love to kind of step back and think about with you, Rachel, what does this evergreen model look like? How do

you balance mission and financial returns, and are there tensions between focusing on high risk, rare disease projects and ensuring enough return to sustain future investment?

Rachel Butler 28:31

Well, we are funded solely by philanthropic capital so people who, perhaps, know how to fund research at a university, but don't have the skill sets to fund that next stage of development, which is, you know, once companies spin out and perhaps are too early for traditional sources of capital, that's where we come in. So, you know, we are very much impact first. We are looking for a significant unmet medical need, an area that, for whatever reason, isn't getting funded, and obviously rare disease, because the small patient populations very squarely fits into that. And then we're looking for companies that may be quite early, but, you know, have a great team, and sometimes early on like that, the team is really all you have to go by, you know, is this the team that can do the hard work to get this over the finish line at the FDA? But we are very much impact focused first, but we also want to get our money back. That's how the system works, and if we can get more than our money back, that's great too, because that funds more companies down the road and future innovation. But we do, you know—we do look to also know that this company has a model and a team and an approach that will be able to get additional funding, as it further develops, gets through proof of concept. We can't carry a company, obviously, we're, you know, a small organization, and we're funding early, but we want to know that it has the potential to bring in additional funding later once it's further down the road. It can be profitable. One of our first investments—we did our first investment in 2019. We have now had eight exits, so proof of concept of the model working. We have our ninth exit on deck, but our very first exit was a rare disease company came out of Columbia University, and they were looking at—they had indications for several rare diseases, and they went public, and, you know, it's had its ups and downs, but we got, I think, overall, a 4x return on that. That's great for us. That's not necessarily great for a typical nonprofit venture fund, but for us, that helps to fund the ones that we know won't work out because we are doing higher-risk investment, but also that gives us funds to go and do more work with more, additional companies. So it can be, you know, you have your risk benefit, but there can be money made in this space. And I would just add, we look for companies that, if you think about rare disease as—I mean, we may want to talk about this later, defragmenting rare disease—but if you think about, sort of the branch of a tree, you've got a thick trunk and lots of little branches going off, if you can, you know, we try and help companies to develop models where perhaps they're focusing more on pathways or mechanisms that are more up the tree to the, you know, closer to the trunk the better, but thicker branches where it has the potential to be able to address multiple rare diseases. And then suddenly you're looking at larger patient populations and something that would be more fitting for venture capital, where you could potentially have stronger returns.

Caitlyn Barrett 32:09

And I do want to get back to defragmenting rare disease. We will get there. I promise. There's one other thing that I did pick up when you were speaking, Rachel, and this is that focus on kind of early stage, and I'd love to turn it over to Adora to kind of think about what BridgeBio is doing with your portfolio model, and looking at both early and late stage development. How are you balancing that?

Adora Ndu 32:33

Sure. No, that's a good question. Maybe where I'll start—just kind of building on Rachel's remarks on, you know, smaller patient populations—our first drug approval was an MoCD type A, and at the time, there were only 400 known patients globally. And since then, we have continued to focus on rare diseases of varying sizes and continue to have the commitment to address some of the most difficult problems. And so when you think about, you know, balancing the financial risk and looking at our NPV models, we do believe that if the science is there, we will advance the program. It might be unconventional. We will look for different ways to do it. And so whether it's within our current model in the commercial space, or, you know, whether we need to establish different models, whether there are nonprofit models that need to be established via philanthropic capital. I think our focus is to advance these treatments. And so historically, we have not deprioritized promising treatments. We will find the best way to advance them forward. And that's the beauty in our portfolio model. It allows us to spread risk. It allows us to spread both development and financial risk. So we're a hub and spoke, we have a central organization with some shared resources, and within our BridgeBio ecosystem, we have subsidiary companies that are developing treatments in disease areas that have very little crossover, and so we're able to sort of separate each of these subsidiaries. They're established with very small teams that focused on advancing treatments forward with as little capital as possible and in as short a time as possible, so that we can get treatments to patients. And that's one of the reasons that we've been able to do so much with so little in a very short period of time. We've also been very creative in how we think about our late stage and early stage development. Right now we have three late stage development programs, two just read out positively last week, and Limb-Girdle Muscular Dystrophy, as well as ADH1, and we also have expected data readout in the first half of the year next year, our early stage pipeline, we actually spun out the vast majority of that just to be able to continue to focus within BridgeBio, on our late stage assets, but also ensure that there's continued focus on the early science as well. So we spun that out in 2024 into a company called GondolaBio, and we were able to raise a significant sum of money so that those early stage programs could continue to advance. We also took a similar strategy with our oncology portfolio. We spun out BridgeBio Oncology Therapeutics also in 2024 and we're able to raise a significant sum as well so that those promising programs can continue to advance. And that company actually went public just a few weeks ago. So we are the—one advantage that we have that sort of sets us apart is the flexibility to really think outside the box, because our goal is getting treatments to patients, and so how do we need to do that? And we try not to box ourselves into one model of doing things really, ensuring that there's flexibility in our ability to move forward.

Caitlyn Barrett 35:55

Yeah, flexibility, evolution. So I actually, I'd love to go to Marshall now and start thinking about clinical trials. They cost a ton. There are lots of pieces there that I think have created a big struggle, because the way they're designed currently just do not suit rare diseases. So can you talk to us about how you're trying to solve that problem?

Marshall Summar 36:21

Well, a lot of it comes down to basic math. So we actually did a, sort of a deep dive on prevalences of rare diseases, kind of across the board. If you look at the recent developments, the groups are getting smaller and smaller and smaller. So probably 80-90 percent of rare diseases have fewer than 150 patients in parts of the world where these trials are being run. That's probably a pretty safe number from that standpoint. So everyone wants to use the classic double-blind, placebo-controlled trial, and the math just doesn't work. You can't pick up a signal because you don't have enough patients to do that, and we're still finding that there's sort of a death grip on that we have to do things that way. But really, there are so many better models. Patient is on control, peer natural history, bayesian assortments—there's so many different models to do that. So that's kind of step one, because if you don't have the right model, you're going to miss your signal. So with a double-blind placebo, even a point five effect size, 50 percent improvement, you're not going to pick it up if you see only have 30 or 40 patients to enroll in your trial, which, for a lot of rare diseases, is kind of where you go out. The other is time. A lot of these companies that are small and are startups—they don't have a long runway, so waiting a year or two to get contracting in place, another year to get IRB in place, because the classic model has been based around the universities. Great example of this would be BioMarin, in their morquios program to get 20 patients, they had to open 40 sites because they didn't know where the patients would be. You actually kind of reverse that and think if you can centralize or have the patients conduct the trial at home, you actually don't have to set up so many sites, which reduces kind of your risk from that standpoint. You can then open up sites later on when you know where the patients are. But that actually can create a big time saving, because on average, it takes a year or two to open up a site and get that so you're already at the beginning of your process. Adding a number of years on time equals money and time equals runway as well too. So by shortening that initial process, you can actually get engaged into the trial earlier. Other things are make it very, very patient-centric. Researchers—and I was a researcher for many, many, many years, I guess I still am. And we get curious, and we want to put two tons of fertilizer in a one ton truck. So it's like, ooh, if I could measure that, ooh, if I could measure that. And, you know, suddenly it's like, well, we're going to have to transfuse the patient before we actually complete the trial. And so you actually have to be very disciplined about what you're going to collect. You need to be very disciplined about your time points. Most of these patients are pediatric in general. That's a very different model from there. So what I would say is thoughtful consideration around the study design using the more aggressive models. The FDA is open to discussions about that, being disciplined about what you collect, realizing that the classic phase one, two, three, and four system is really—I think we're going to have to just discard that. In rare disease, you're going to see one-two, two-three, two-three-fours. Take your pick. Your pivotal may be your first foray, because you may only have handful of patients. Smallest trial I've done had five patients, and we actually were able to get approval on that with only five patients. And I remember the FDA statistician looked at me and was like, that's not representative of the population. I said, no, that actually is the population. There are only five patients, and his eyes kind of rolled back in his head, and he chuckled, and said, okay, let's figure this out. So they—people will work with you. I think there's sort of a fear of the FDA, fear of being told no, as if somehow that's going to make you carry around a scarlet letter around your neck, and the FDA won't talk to you anymore. Ask them, push. They are actually—they don't wake up saying, we don't want patients to have therapies. They will not always. There's a practical joke department there some days, but by and large, they will work with you. Sorry, that was a little longer than you probably wanted.

Terry Jo Bichell 40:30

One thing you said, time is money, but for the patients, time is also sickness. We do not have time to waste. These kids if they get treated early, they might not regress, they might not have arrested development. Time is of the essence for all of these groups. And there was one other thing you said. What I've noticed is that our industry members are often more hesitant than our FDA contact.

Marshall Summar 41:01

Absolutely.

Terry Jo Bichell 41:02

The FDA is willing to try a lot of new things, but the industry partners are scared to do it, and so I think what you're doing is just fantastic.

Marshall Summar 41:11

Well, thank you. And we're, for instance, we're running a Friedreich's ataxia trial right now, and it's public knowledge, so I'm not breaking any NDAs, so if anyone from Larimar is here, don't shoot me.

Caitlyn Barrett 41:23

Oh, you can do it in here. No one will share it.

Marshall Summar 41:25

Oh yeah, sure. But these are patients who are, in real time, losing control of their bodies. And it was interesting when we finally got the enrollment open, we filled every slot in that trial in two hours after enrollment was. I mean, the pressure on that community was so great, and then they had to go on a pause because of a reaction for one patient. Everyone was calling us every day saying, "Are we reopen? Are we reopen? Are we reopen?" And so one of the things—and this, I'm coming out of a clinical background, I can sort of appreciate this—there is tremendous pressure on these families to make something happen now.

Caitlyn Barrett 42:05

Giacomo. Terry Jo called you guys out. Talk to us.

Giacomo Chiesi 42:09

Well, a little bit right? I think, Marshall, you mentioned a lot of things, but I'm going to pick two of them, right. How do you compress timelines and how do you derisk, right? So on compressing timelines, Terry Jo, you mentioned that the FDA, and I will say other regulators as well around the world are willing to try a lot of different things, right. So if you want to compress things, one of the aspects from an EMA European perspective is you might want to go for the prime designation, where you can have a continuous collaborative dialogue with the agency, and probably cut your costs and cut your timelines. The FDA has recently started talking about RDEP rare, I'm sorry—Rare Disease Evidence Pathway, which could be a potential new pathway, applicable in case there is no approved therapy for a specific indication, and in the context of a potential accelerated approval, where potentially your biomarker would translate into a clinical endpoint. As well as, if you think about Japan, the Sakigake is another mechanism for you to expedite and even in China, recently, a new free trade area was introduced for drugs that had been approved, for drugs to actually be imported directly in the country. So there are ways for companies to expedite. From a derisking perspective—I think Adora you covered it extremely well—having the patient journey completely interwoven in your clinical development so that you can get patient advocacy organizations input at the outset, during your preclinical testing, before clinical development starts, and making sure that patients are engaged throughout the process, making sure that you continue to adapt your clinical development to their needs. That's going to be risk, because it's going to expedite and it's going to reduce the chance that, for example, patient participation in your trials is smooth or very small. So there are ways for us as a community to come together collectively to accelerate development and derisk it.

Marshall Summar 44:13

And let me add on what he's just saying, because that's spot on. There's also some really good mechanisms. The FDA has the interact meeting, the EU has—EMAS has the I think it's scientific advisory—I can't remember the exact name—but it's actually a nonbinding meeting with regulators, so they can actually approach it as scientists, as you know, and—you can get opinions instead of the agency agrees that discussion. It's the, what do you think about this? We thought about this as an outcome marker. Is this something that could work and they'll actually have a discussion with you, and you can have back and forth input. It's a really powerful thing. It's pretty new, and I think a lot of folks aren't aware of that, but it's about the only time you can actually have I wouldn't call it a casual conversation, but a casual-esque conversation with the FDA.

Adora Ndu 45:02

Well, you know what I would add to that is, and I've said this before, with over 10,000 rare diseases, we cannot expect the FDA to be experts in all of them. And so when we think about all of these mechanisms to—that we have available to us to interact with FDA, a big part of that is the coeducation from industry, from patient organizations, for us to bring the FDA along with us with the science, to bring the FDA along with us with the patient journey, so that as we are generating data, as we are deepening our knowledge about the disease there as well. And so those interactions are really important. I know some companies are

more keen to go to the FDA and try out different things or be a little bit more innovative. It's so important to do so, to have those conversations and to understand the whys behind their feedback and their reasoning and to push a little bit. You know, I think it's easy to fall back on conservative, but in rare diseases, we have to be innovative. We have to push the envelope.

Marshall Summar 46:11

You will fail with conservative, that's the thing. And you need the Terry Jos at the table, because not only can they educate the FDA about what's the impact of this disease on us? What's the important outcome to us? You know, it's—there are so many outcomes that are these sort of artificial constructs, but you really need more. What is a good real-world impact of a treatment of this disease?

Adora Ndu 46:33

Just really quickly, I just reflect on an example in a prior life where to the agency, the particular disease in adults was not one that was burdensome or considered a serious disease. And, you know, they were open to having a patient and industry meeting, large conference room that was completely full of KOLs, patients, and members of that particular company, and went around the room and heard from every patient, every investigator, and at the end of that meeting, I think the agency walked away really enlightened in understanding and really, like, kind of contextualizing their understanding of the disease directly from the community and directly from the providers that treat the patients. And so that becomes really important, because many of the reviewers haven't actually seen or treated a patient with most of these diseases, and so being able to have those conversations is critical.

Caitlyn Barrett 47:33

I think. Yes, please, Terry Jo.

Terry Jo Bichell 47:37

Yeah, so we wanted to create another opportunity for industry and patient advocacy groups to speak back and forth with the FDA in one of those casual-esque type interactions. And so we're actually—we've organized a research roundtable on neurodevelopmental disorders. Neurodevelopmental disorders, rare genetic ones, are the fastest growing rare diseases, something like 70 percent of rare diseases, it turns out, are neurodevelopmental disorders, and they're notoriously difficult to measure any kind of treatment effect. So we've got to open up dialogue on that. And so this coming year, October, it'll be our first one, and we're having this research roundtable, which will be an open dialogue between all these companies, these patient advocacy groups, and the regulators, and also from the EMA too, to try to see if we can come to consensus and come to agree on some of the things that we can measure and move forward.

Caitlyn Barrett 48:42

I think that you're going to have a few people coming to see you after this panel. I'm going to move to the Q&A from the audience. I was encouraged at one point to ask for more questions. I don't need them. This is—you all are so engaged. Thank you so much. The first one I'd like to get into is thinking about kind of some models that have worked in the past. We've mentioned a couple of them. On the fundraising side, someone asked, "Are there examples of savvy ways patient advocacy groups raise significant amounts of money to support therapeutic development (i.e. is the Cystic Fibrosis Foundation model, reproducible and scalable)?"

Marshall Summar 49:26

I actually worked with CF when they were first doing their database. Preston Campbell, who was later on the CEO, worked together with me at Vanderbilt. And that is—that's a wonderful model. Friedreich's Ataxia is another. There are a number of good models out there. The problem is that is a little bit of a unicorn. There were enough people being impacted. There were enough high-profile individuals with family members where they were able to build up funds sooner. What I would actually say is there's safety in numbers. So if you're in a very small, rare disease community look at who your nearest neighbors are. When you talked about going back up the tree and getting things closer to the trunk, see who else is on your branch. Pooling resources is actually a very effective way. Outcome markers may be very similar from disease group to disease group. Therapeutic models may be very similar from disease group to disease group, you know, even the patients where, what we call the in of one community, have banded together to actually try to develop things, even though each patient may have an individualized therapy, there's enough similarities where those patients have actually started pooling resources. So I would say pooling resources is a pretty good model, and it's kind of the BridgeBio model in some ways too.

Giacomo Chiesi 50:41

I want to make a comment in relation to this, because one of the things we haven't spoken about, but I think it's one of the elephants in the room, is the scarcity of capital these days. Because a lot of the capital has moved out of rare diseases, especially out of cell and gene therapy, over the last two, maybe three years. I don't know that there's a specific solution to it, a silver bullet, but for sure, in our experience, blended finance that you know puts together the vision of public institutions, the drive of private companies, and the passion of philanthropy could be one of the answers. At early stages, where you have no proof of concept, mechanistically, you don't know where you're going, you don't have a good understanding of the disease. A lot of that is going to have to piggyback on that early stage philanthropy, if you will. There are models that we've seen working to potentially pick up programs that have already evolved and that have been left stuck in the middle, if you will. We at Chiesi are actually a proud cofounder of the Orphan Therapeutics Accelerator Fund, which is a not-for-profit, completely philanthropic venture fund whose aim is to basically pick up and fund programs that have been left, that have been shelled by pharmaceutical companies just because there was no market. Just because there were too few patients. We think this is one of the models, not the only one, and ultimately, we believe that

blending, that blended finance model, is going to have to be part of the equation here to potentially get to a solution where we're not going to leave any patient behind in the future.

Rachel Butler 52:20

Just on that point, there are examples of smaller drug development or biotech companies that license or in license therapeutics that have been developed to a certain point by big pharma, and then whether that program's been discontinued or it may not have been effective for the specific disease that they were looking to treat, but it's been through a phase one trial. And we are invested in a company that has done that, and they have, I think, now, three drugs. The first one they're developing is, it's for pediatric cancer, but it has been through a phase one, so that shortens the timeline, shortens the expense. They're still struggling to raise money. Much of it has come from, you know, grants from disease-focused foundations or impact funds like us. But, you know, out there, day-to-day, just working at it, I think there are close to 20 million raised. So, you know, there are ways to derisk a little bit, to shorten the timeline, and that also helps to bring in funding.

Terry Jo Bichell 53:31

There's—this is not a COMBINEDBrain effort, but it's a lesson from the Angelman world, the Fast Foundation for Angelman Syndrome Therapeutics. They've organized an entity called AS2Bio, which is a for-profit investment arm, and they have at least five different treatment modalities. So when someone invests in that, they're investing in five different shots on goal, and if one of them makes it, then they get a return.

Caitlyn Barrett 54:06

What I know, Marshall, I'm so sorry, Giacomo—you mentioned Giacomo. I forgot what I was going to say to you. Marshall, go for it.

Marshall Summar 54:17

It's actually something Giacomo was saying. If you actually look at the development of the rare disease community early on, when there were very few products, the ROI was really high. We could afford to be inefficient. We could afford to be wasteful in the cost of getting rare disease therapies done, it was about two thirds of what a regular drug would cost for a fraction of the number of patients. When you start getting up around a thousand currently approved FDA drugs for Orphan Designations. Then that ROI changes, because you're getting pushback from payers. It's about 18 percent, I think, of global drug sales. So suddenly it's noticeable, and you start to get downward pressure, which I think was adversely affecting investment in the field, maybe more so than just capital lacks. And I think that's why we have to really look

at becoming more efficient, changing the model. Everything every one of these folks is doing, is doing that, and I think that's where we have to head.

Caitlyn Barrett 55:13

You got me back. Thank you. I'd like to talk about incentives, if that's okay. I would like to talk about the priority review voucher and anything else you'd like to discuss in that realm, but with limited capital, we need to be thinking about how we can incentivize rare disease drug development. So, Adora, would you like to share a little bit of that context?

Adora Ndu 55:35

Yeah. I mean, with the priority review voucher, both for for profit and nonprofit entities involved in developing treatments for rare disease, it's critical. When we build our NPV models, we do factor in the voucher. With our first approval, as I mentioned, in an ultra rare disease with 400 patients globally, we did receive the voucher. We were able to sell the voucher and reinvest it across our pipeline. So it has played a pretty meaningful role for a company of our size and of our tenure, in helping to advance drug development and be able to grow and do more with less and so we, along with many others in the community and industry, are very hopeful that the PRV program will be reauthorized, because it's actually really critical to drug development in the space. Giacomo mentioned some work that he's doing with the Orphan Accelerator and at BridgeBio, we spent a good part of 2024 really running down the idea of being able to stand up a nonprofit biotech company that would essentially take drugs off of the shelves across many different companies and advance them forward, leveraging philanthropic capital primarily, but also leveraging proceeds from the sale of a voucher and structures such as that are going to be really dependent on the voucher program being viable and being sustainable, so that investments can be—essentially, you're able to create a flywheel where you can reinvest and continue to expand the efforts and develop more treatments for rare diseases.

Rachel Butler 57:10

I think from a funding perspective, it changes the entire risk benefit equation. So if you're looking—so just in case not everyone may know what it is—if you are successful getting a drug approved for a rare disease, one of the incentives that has been in place is that you get a voucher that accelerates your next drug development, potentially by six months. You can sell that to a big pharma that may have a blockbuster drug where six months is worth billions, but to the rare disease company, it's sort of this—like, if we can get over the finish line, we have an additional 100 million. That is a big incentive for an investor. Right now that voucher program has expired. It would be a really good thing, I think, for Congress to come back in session now, and that would be a great thing to work on is to reauthorize that, because it was a win-win for everyone. You know, it didn't hurt the FDA to work a little, you know, accelerate something. It was great for the small company developing the drug, it's great for pharmapayers.

Adora Ndu 58:13

Cost taxpayers nothing.

Rachel Butler 58:16

And cost taxpayers nothing and the fact that that's been allowed to expire is really hard to understand.

Giacomo Chiesi 58:21

Okay, completely agree. I just want to bring one additional equation here to the topic which these PRVs used to be sold between $100-120 million each, right? And now there's obviously very few of them, because the program has not been reauthorized in September 2024, so now these vouchers go for maybe $150 million. Okay, if you're good at what you do and depending on the program, right, but you can potentially develop a drug from beginning to finish, basically for $40-60 million so you divide 150 times that figure, you get three, four, maybe five, new rare disease drugs with a PRV. The absence of it means that 3,4,5, rare diseases are not going to have anything yet. That's the immediate societal impact if you don't have that.

Caitlyn Barrett 59:14

Yeah, I really appreciate that math that was easy for me to do in my head, but really critical for us to all understand the importance of the voucher. We are very close to the end. So I would like to do a quick popcorn question to each of you. I want to end on hope, always. What's one opportunity within reach that could transform how we approach rare disease? Can we start with you Terry Jo?

Terry Jo Bichell 59:41

Sure, I think the precompetitive pathway is the one opportunity. All these companies are going to need to share controls. They're going to need to share biomarkers. If they pitch in just a little bit of money, they get pennies on the dollar investment back. In those shared data and shared resources. So I think that's a game changer, and that's what we're trying to do.

Caitlyn Barrett 1:00:07

Absolutely. Rachel?

Rachel Butler 1:00:09

It's amazing we've gone a whole hour without talking about AI, but I guess I will bring that up.

Caitlyn Barrett 1:00:14

I failed!

Rachel Butler 1:00:17

In that, you know, AI—we're already seeing that with companies that we're looking at where they're using AI platforms to look at, you know, thousands and thousands of drugs, to look at particular mechanisms of action or pathways, or, you know, existing drugs to repurpose them, which we didn't get to talk about, but that might be useful for a rare disease. So I think we're going to just see, suddenly, just breakthroughs in that area of identifying potential drugs and drug targets.

Caitlyn Barrett 1:00:45

So critical. We should do another panel next year. Giacomo?

Giacomo Chiesi 1:00:49

I'll be quick, and I don't have much to add, because a lot of things have been mentioned already. But I believe that if every company really had an unwavering commitment to patients, and the patient journey was embedded in drug development ever since the beginning until the very end for every company that will make the industry so much more efficient and would accelerate a lot of the development for rare disease drugs in the future.

Caitlyn Barrett 1:01:14

Thank you. Adora.

Adora Ndu 1:01:15

I think we've each touched on the challenges in raising capital, especially in the very small populations. I do think there's a role for public-, private-, megafund for rare diseases. And, you know, if that's something

that could come together, that could be leveraged for, especially the very small populations, as an opportunity for capital, I think that could make a big difference.

Caitlyn Barrett 1:01:36

Wonderful.

Marshall Summar 1:01:37

Well, that's the problem with being last.

Caitlyn Barrett 1:01:40

It's all gone. No, you can come up with something.

Marshall Summar 1:01:43

I would say the biggest thing I see, the biggest advantage right now, is actually the acceptance and the involvement of the patient community in the process. That I think is one of the most unique things that is going on in rare disease. I also think it's one of the best drivers. It's also something where you have to kind of watch what you're doing. But I think that actually is the really unique thing that is going on that really is pushing the field forward.

Caitlyn Barrett 1:02:06

I truly will walk out of here with about a hundred things that I want to do. I hope the same goes for everyone else in this room. Let's get back together and think about how we can activate. I am so appreciative of everyone's time. Thank you for being here this morning, and thank you so much to the speakers. [Applause]