PARENTS AND PATIENTS AS PIS: THE RISE OF FAMILY-LED SCIENCE

Announcer 00:04

Welcome to day two of the Milken Institute Future of Health Summit. We are delighted to have you join us today and look forward to your participation throughout the day. Please welcome the panel to the stage.

Sylvie Raver 00:23

Hi. Thank you for being here. Good morning, everybody. Bright and early. Welcome to "Parents and Patients as PIs." This is going to be a conversation focused on the unexpected and increasingly influential role that parents and patients themselves are playing to accelerate progress in rare diseases. Thank you all for being here. I'm Sylvie Raver. I'm a managing director at the Milken Institute, where I lead SPARC, our Science Philanthropy Accelerator for Research and Collaboration. Patients and families affected by rare diseases often receive a diagnosis, only to find themselves with very little support as they navigate what comes next. They may find a patient community or an advocacy group. They may even connect with a handful of scientists working to understand their specific disease. But the one thing that they desperately want and deserve—a treatment—remains out of reach. Rare-disease families are all too familiar with how the cards are stacked against them, and we'll hear more about that today. Pharmaceutical companies and investors often see little financial incentive to develop treatments for such small communities. Scientists who want to study rare diseases or develop potential treatments struggle to secure funding. Research dollars, especially government funding, tends to go to more common diseases. Even the regulatory pathways designed to ensure the treatments are safe and effective can present challenges because they were built around large patient populations with methods that may not work for diseases, especially with such heterogeneous presentations. Despite the profound impact that these diseases can have on families, public awareness and government attention also remain low. These are systemic obstacles that make developing treatments for rare diseases extraordinarily difficult and different. But as one of our speakers, Ethan Perlstein, recently wrote, "Sometimes fate messes with the wrong person," alluding to a subset of rare-disease patients and parents who are natural-born entrepreneurs and innovators and refuse to take no for an answer.

Sylvie Raver 02:13

We're lucky to have a few of these extraordinary people on the stage today who've recognized the tremendous unmet need, built programs to accelerate research, and bring us closer to treatments for patients and families. All four of our panelists have incredible accomplishments that have advanced the rare-disease space. In our discussion today, we'll learn about their experiences, how these experiences shape your work, and what they've learned along the way. More importantly, we'll discuss the lessons learned that they're bringing to make the journey easier for the rare-disease patients and families who come next. So, I'm delighted and really honored to introduce our panelists today. Sunitha Malepati is the founder and CEO of the Buffalo Initiative and vice president and treasurer of the CACNA1A Foundation. After her daughter's CACNA1A diagnosis, she built the Buffalo Initiative to serve as a scalable, investable platform dedicated to patient-led ultra-rare drug development. Thank you for being here. Ethan Perlstein is CEO of 1000 Cures. A molecular and cell biologist by training, Ethan founded Perlara, the first biotech public benefit corporation, which focused on drug discovery for rare disorders. Now, through the 1000 Cures initiative and its innovative funding model, he works with many rare-disease communities to make parent-led successes repeatable. Terry Pirovolakis, CEO and founder of Elpida Therapeutics. After his child's SPG50 diagnosis in 2019, Terry cofounded CureSPG50 and led fundraising and research that resulted in a gene therapy treatment for SPG50 patients. He's now developing rare-disease gene therapies at Elpida Therapeutics for several other ultra-rare conditions. And Mitzi Solomon, founder and president of Countdown. A communications strategist, Mitzi was inspired by her own patient journey to build Countdown, which is a nonprofit working to accelerate mitochondrial science and medicine across rare and common diseases. Can't wait to hear what they have to share with us today. So, thank you all for being here. Sunitha, I'm going to start with you. After your daughter's diagnosis, you joined the CACNA1A Foundation's board, we talked about how it's still very near and dear to you, and went on to found the Buffalo Initiative as an attorney and a parent, rather than a biotech entrepreneur. How has your background helped you build Buffalo, and what makes it unique?

Sunitha Malepati 04:27

Yeah, sure. Thank you so much for having me today. I'll just start by sort of going back to the basics. I never thought I would find myself in rooms like this, on panels like this, talking about rare disease. As you mentioned, I went to law school, and I felt like I was minding my own business. I was a private investment funds attorney, and prior to that, was working in philanthropy around innovative financing for social issues. And I had my daughter, who's now nine, and along the way, realized there was something going on with her that was different than my son. We got her diagnosis after almost three years of searching for an answer and realized that for a lot of these diseases, you can get a diagnosis, you can see this really promising science out there, but then there's no next step. There's just this valley of "Here, live with this news." And so, as a parent, it's not something that you can accept. And there's so many amazing entrepreneurs in this space because they have been dealt this hand, and I know a lot of you all are going to talk about this. But what I kept seeing over and over again was patient groups forming and sort of reinventing the wheel and trying to build out the exact same infrastructure, getting funding from their own communities. And I started to think back on my work building and advising clients who were building private investment funds and thinking about philanthropists and other impact investors and what they were doing in other spaces like climate tech and affordable housing, and all of these areas where the markets fail us. And why wasn't that happening in rare disease? We have this incredible science. It's not reaching patients. We have these commercial viability issues. So, we need to develop alternate structures. And so, that's really what led me to try to build out this effort called the Buffalo Initiative, which is really

focused on trying to build out sustainable funding pools with impact capital, private capital, and philanthropic capital, along with building out the shared infrastructure that all of these groups actually need to drive drug development, because they're not going to be able to rely on the traditional biotech or biopharma partner to do that for most of these ultra-rare diseases.

Sylvie Raver 06:46

That's incredible. We'll hear a lot more about it as we go on. Thank you. Ethan, you've seen these challenges from many sides as a scientist, a founder, an investor, and a foundation CSO. Can you tell us a little bit about what 1000 Cures does and why you choose to build it alongside parent-led programs?

Ethan Perlstein 07:03

Happy to. So, 1000 Cures is the world's first start-up accelerator that backs rare-disease parents who start biotech companies to cure their kids and other kids like them. And after what you've just heard, and maybe some other things you've heard in the past, you might say, "Well, wait a minute. I thought rare-disease drug development was economically impractical, let alone never will be profitable." But there's three magic letters that, I think, put a stake in the heart of that zombie lie, and those three letters are PRV. Say it with me. Priority, review, voucher. This mechanism allows pharma's insatiable appetite for new blockbusters to be coupled to the development of new medicines for kids with rare diseases. And so, 1000 Cures is all about empowering with capital and guidance and know-how the founder parents that you see on the stage, the ones that I can see in the audience, despite the blinding lights, and others who are not in this room, maybe on this livestream. So, with my cofounder, Ryan, we started 1000 Cures six months ago and have scoured the world basically for what we call FAMCOs—family-founded biotechs. And there's examples of ones here and out there, but we want to see many more of these in the world. And we like to think about 1000 Cures as Y Combinator for rare. In the same way that YC empowered a generation of overlooked and undervalued founders 10 years ago, the people like Sam Altman who are now running the world were once seen as insignificant pipsqueaks who didn't have a place at the table. You had MBAs from Stanford who were supposed to run these companies. And you hear a lot of the similar talk in biotech about, well, it's nice to have the rare-disease parent there, but are they really taken seriously as an equal, as a co-developer? So, that's the thesis of 1000 Cures, and hopefully you can help me spread the gospel.

Sylvie Raver 08:53

Absolutely. What we're doing today. Terry's one of those archetypes. He brought something completely different, a career in IT, not biotech, and led research that treated three children in three years. That's incredible. Tell us what you built and what you wish every parent or patient starting this journey knew on day one.

Terry Pirovolakis 09:11

Yeah. So, Michael was born December 2, 2017, and on April 2, 2019, after an 18-month diagnostic odyssey, he was diagnosed with a disease called SPG50. We were told, "Go home and love him. There's nothing we can do. He'll be paralyzed from the waist down by the age of 10, quadriplegic by the age of 20, and he'll never walk and never talk." We went home and lost our minds, and I said to my wife, "We have to do something. We can't just sit back and watch this beautiful child fall apart." My wife said, "Let's just go all in." We liquidated our life savings, went down the path, found an amazing team, and decided that we were going to do everything concurrently. So, while we were testing the mice, we were doing toxicology. While

we were doing toxicology, we were manufacturing the drug. While we were manufacturing the drug, we were applying to the FDA and Health Canada. And three years later—just under three years—we treated Michael, and then I tried to give the drug away, and no one would take it. I tried the NIH, I tried different foundations and companies, and because there were only 100 kids in the world, they said it's too rare. Even though I had drug product in the freezer, we had a Canadian health regulatory application. So, I decided that we had to do more. And the day that Michael got treated, a family from North Carolina called me and said, "My child has this disorder as well." And we decided to open up an FDA submission. We did so, treated two children, and since then, now we've treated 19 children with SPG50. We took on three more programs, CLN7 Batten, CMT4J, and now Lafora. And by Q1 of next year, we'll have treated 48 children around the world. And then we'll also be dosing another 50 to 100 with Lafora going on year two and three. And we're also applying to the FDA for a BLA for our SPG50 program, going through the commercial process, which is a significant process. And thankfully, the team on here from the FDA yesterday was trying to change that, because if we try to get to the end right now, we're all going to fail. It's an impossible task for us to get there. So, we definitely need an alternate pathway.

Sylvie Raver 11:11

Yeah. Yeah. A lot more to talk about there. Thank you. Mitzi, your own experience as a parent led you to start Countdown. How did that experience shape your decision to elevate an entire field of science rather than focus on a single disease like some of these folks have?

Mitzi Solomon 11:27

My personal experience is not only being a parent, but actually a patient myself. I've actually had complex health challenges my entire life. From the moment I was born, I had a heart defect. I was very low tone. Always throughout my life, I would have a lot of energy. I would go, go, go, and then I would crash for days, and then I would just somehow bounce back. Always had a lot of muscle atrophy. When I became an adult, four kids later, after my third son was born, 45 minutes after he was born, I had a stroke. And no one believed that it was a stroke until they actually did the MRI on my brain. But at first, they said, "You know what? It's a vagal response. You've had three kids, three years. One push, that's all it's all about. You're fine." But of course, it was a stroke. I ended up having a lot of therapy. I continue to have therapy for that. Then I was crazy enough to have a fourth child. And my daughter was born, and she was born not breathing. And that's where you turn from always looking within, wondering what's going on with you, and caring more about your child and saying, "I don't understand. If all these things are happening to me and now I have a child who's having all these difficulties, what's next? Is it genetic? Is it something that we can prevent down the road?" So, she was born not breathing. She ended up having laryngomalacia, so we had to do a supraglottoplasty to open up her larynx. She was aspirating. She was severely low tone. Nine surgeries later, and being on a feeding tube for a while, she was able to get off and do better. But the point is that after she ended up having all these health issues, then I was running on adrenaline, and my body just continued to crash. And it crashed so bad that I ended up needing to seek help. But I would go from specialist to specialist, doctor to doctor, and everyone would pawn me off to the next person. Everyone was treating things system by system, organ by organ, treating the symptoms, and not recognizing that all of these things that I've been diagnosed with, from dysautonomia, mast cell activation, Ehlers-Danlos, mitochondrial dysfunction disorder, celiac, they had to be connected. And so, I started doing all the science and digging into the science myself and recognizing that we should be looking at everything through a mitochondrial lens. Mitochondria sustain life. It's everything from your heartbeat to your thoughts, to how you move. And why aren't we looking at things through that lens? So, that's where Countdown was born. I

knew that we needed to look at science differently, and we need to be treating patients differently. And not only treating and preventing disease, but also when it comes to health optimization and prevention. And so, that's really how Countdown was born. I gathered the best scientific and medical advisory board and decided to really build out the organization where we're looking at all health and all disease through that lens.

Sylvie Raver 14:23

That's incredible. You've all taken this journey from advocate to leader of these different initiatives. I want to talk a little bit more about that transition and what you would want to share with others. I'll start with Ethan. You've invested in about 100 companies and seen all kinds of founders. What do parent or patient founders already bring to the table? What is unique to them, and where do they most need support to succeed? How should the field back them in ways that you've really seen and are moving into action?

Ethan Perlstein 14:50

Yeah. The rare-disease parent founders I know share all the attributes of the best entrepreneurs, period. But obviously, they are driven by something that no other entrepreneur, depending on—really is ever driven by, which is the love of their child. It's a force more powerful than nature. So, I think my perspective is that every single rare-disease parent, when they get that crushing diagnosis, has some kind of entrepreneurial potential. It's simply a matter of can they get over their imposter syndrome? But there's also practicalities, like they might have an unaffected child; they might have to support other family members; they can't quit their day job. But for the ones who are able to take that leap, they are in the same league as, I think, the most extraordinary founders. And I think the thing that needs to be maybe pushed back on from the trad bio perspective is that, well, maybe there's this idea that if you're too much involved, if you're too emotionally involved, maybe you're not going to be unbiased. You're not going to make the right business decisions. And in my practical experience, that never really comes up—and maybe someone like Terry can comment on this—but I think that's the biggest pushback: it's not just that the parents and the advocates can have a place at the table, but at the end of the table, where the advocacy stuff conversations are happening, not where the business conversations are happening. And I want to break down that wall entirely.

Sylvie Raver 16:17

That's really helpful to hear. Kind of taking what may be considered a vulnerability and turning it into a strength. Terry, you want to comment on that? Maybe a way in which your approach has benefited from your own experience here?

Terry Pirovolakis 16:27

Yeah. I'm helping several hundred families actually at this time as well, and what I find is you have to understand that a lot of these people that are helping us out are doing so on their own time, at their own pace, and even though you sign a contract with a university, that person might be only 1 percent of their fraction of their time giving to you, but they're giving 80 percent of it. So, you have to put it in perspective that you can't go and freak out on this individual when something goes wrong because it may not be their problem, and that we have to always relate it to keeping things professional. I find a lot of times when families will go on there and be like, "Oh my God, the mouse died, and this happened," and they just completely lose it. You can't do that. You have to be a professional. You have to think about the approach

and move forward. Otherwise, what's going to happen is people are going to lose interest. They're not going to want to work with you. They're just going to move on. I think it's really important that we have to always keep perspective.

Sylvie Raver 17:18

Yeah. Channeling the passion into a—I could see how it could potentially—

Terry Pirovolakis 17:21

Somewhere else potentially. You know?

Sylvie Raver 17:23

That's right. Finding another outlet. Sunitha, patient-led means different things to different people. From the programs that you oversee at Buffalo Initiative, can you talk a little bit about what it looks like families that you know are really in the driver's seat? How does it make a difference to the outcomes that you're seeing?

Sunitha Malepati 17:40

Yeah, just building on what Ethan already said, that these are incredible entrepreneurs that are driving real scientific progress despite their backgrounds, mostly because of just this incredible passion to make a difference for their child or their community's well-being. And what is so incredible about these individuals is they are solely focused on what it means to bring that incredible science to the patient or to their loved one, and that's so different than everyone else involved in this entire ecosystem. I mean, there are incredibly passionate researchers and clinicians and biotech companies, but they have slightly different incentives than the patient or community themselves. And so, when you have someone leading who's solely focused on that end goal, the work gets done differently. It happens at a fraction of the time and cost that traditional drug development happens. And so, having families really in the driver's seat makes an incredible difference to this entire process, and we have so many examples of that happening all around the ecosystem. And what we really need to be doing is supporting this innovation to happen more at scale.

Sylvie Raver 19:03

Mitzi, you're doing that too, with bringing these multifaceted teams together. You've got scientists, clinicians, philanthropists, brands, advocates around this shared belief. Can you talk about how you're getting such different groups to buy into this shared vision, practically?

Mitzi Solomon 19:18

Yeah, absolutely. Well, the first thing is when we started, most people didn't even recognize that mitochondria played the most pivotal role in our body. So, first, we had to explain what mitochondria was beyond seventh- or eighth-grade biology, and then also recognizing that mitochondria had more to do than just with rare disease. It had to do with everything. And so, education was number one because without education, people aren't going to understand why you're focused on health and disease through a mitochondrial lens. The other thing is knowing that people need to be not only smart patients and really understand what's going on with their own bodies, but also smart consumers. So, that's why we also built

out a brand program, because we recognize there's a lot of bad actors out there. And right now, coming online, there's a lot of technology, there's a lot of products out there, supplements. They all say that they are there for mitochondrial function and to boost mitochondrial function, but they're not all equal. And so, that's where Countdown comes in, and we really want to be responsible and make sure that we are giving our patients, anyone that's involved in our community, a better understanding of what's going out in the marketplace. And then as far as when it comes to science, one thing that's important to know about rare disease is a lot of the projects that we fund that are in the rare-disease space is also because you want to start with rare disease. It's easier to get to common disease when you're starting with a smaller population. And so, whether it's the projects that we funded on MPAN, Barth syndrome, and Friedreich's ataxia, or we're working on a hypoxia study for Parkinson's and cancer, what we want people to recognize is that they all can work together and they can overlap. One of the things that we have funded is mitochondrial biomarkers. We actually funded the first ones out of Israel. It tests mitochondria's quality, content, and function. Now, that is a project that we funded that actually can benefit all areas of science and all the projects that everyone else in this room is considering being a part of. And so, for us, it's all about building on each project, making sure that we complement—all the work that we're doing is complementary—and that we're able to be open and share with others, so that way we can build on the science together.

Sylvie Raver 21:32

Thank you. So, let's talk about what families are getting right, and then maybe where the traditional pathways still have a bit of an edge. I'm sure each of you have a perspective on this. So, each of you have moved quickly. Terry, I'm going to start with you because you've made tremendous progress in such a short amount of time relative to what we think of the traditional timeline. So, let's dig in a little bit to where the traditional system still has an edge. You have taken on some risk that maybe others have not. Where could regulators better support parent-led programs and help distribute that risk in a way that didn't feel so imbalanced, maybe?

Terry Pirovolakis 22:07

Yeah. So, I think the FDA is doing a really good job right now of giving guidance and support for N-of-1s and small programs. Every interaction we've had has been excellent. So, I think from the regulator's perspective, we have a path. I think we have a path forward. I think what people lose focus on is partnering with the right teams, right? They go to a team that maybe has found the disorder or is doing cell biology on the disease, but they have no understanding of how to bring a program to the clinic. And what happens is they'll get to a certain point, they'll apply to the FDA, the FDA will say, "You missed something," and then you have to go back, like Monopoly, back to Go, and then go forward again. So, I think the biggest thing is partnering with the right team that knows what they're doing so that you can have a clear path forward. And there's going to be hurdles along the way, there's no doubt about it, but as long as you find that team that brings you there, you're going to get to the end. And I think that as long as you follow that pathway, then the FDA's pathway will be a lot easier as well.

Sylvie Raver 23:06

Ethan, would you like to expand on that? What some of the parent-led programs have in common, what do ones that succeed have in common with building these teams? What are some practicalities that you've seen really ensure success?

Ethan Perlstein 23:19

Is it for me?

Sylvie Raver 23:20

Yeah. Did I say Ethan? I'm sorry.

Ethan Perlstein 23:21

Oh, sorry.

Sylvie Raver 23:22

I was just staring at you.

Ethan Perlstein 23:23

I think, to Terry's point, the most successful operators I've seen, they try to avoid a lot of first-time mistakes. And I think they listen to their elders, and when it comes to—maybe you shouldn't—hate to say it—maybe you shouldn't work with that PI, or maybe you shouldn't try this modality, or maybe you should be placing two bets at once. Maybe you're going all in on this, but what about a backup plan? So, I think the truth is a lot of these parents are already conferring and conspiring with each other behind the scenes. There are Slack channels, there's WhatsApp groups, there's texts, and people are swapping intel just the way that business executives are swapping intel from their perspective. So, I think, to Terry's point, if you're starting out on this cure odyssey, the first thing you have to do is do your diligence, and that means talking to the groups that have already cooked and figure out, how did they do that? How did Terry work so fast? How did he—and you're going to realize that he probably encountered some obstacles.

Terry Pirovolakis 24:21

Oh, sure.

Ethan Perlstein 24:22

And then maybe if he can spare you that headache, then that's a rising tide that will lift all boats.

Sylvie Raver 24:28

Sunitha, would you like to expand on that?

Sunitha Malepati 24:30

Yeah. I'll just comment. Nasha Fitter was originally supposed to be on this panel, and I think one of the things that she did so incredibly well in this space, and is going to help so many different groups, is build out a different way to do natural history studies. And I think that the traditional way of doing business in this space doesn't always work for families. And she saw that in this one space where all of us need natural history study data. It's very expensive. It's very burdensome on families to go into a clinical site to do that on a regular basis. And she, with her company, Citizen Health, has developed a way to develop natural

history from electronic medical records. And that was born completely out of her lived experience as a parent of a child with FOXG1 syndrome and realizing it wasn't going to be possible to travel with a severely impacted child on a regular basis to do that. And not only that, you're just not going to have families scattered all over the world be able to contribute their data in that way. And so, I think what is so amazing about what rare-disease parents and communities are doing is they're building these innovative tools that are going to eventually benefit other programs outside of their own. And that's completely built off of that lived experience, which can inform the—it should inform this entire drug development journey, but it doesn't always.

Sylvie Raver 25:54

Thanks for bringing up the Citizen Health. That's a really great example. Can you share a little bit about your model and how that is providing some of the resources so that people don't repeat the same mistakes, like you guys are saying? Learning from your—you're not an elder, but learning from others who may have trod this path before?

Sunitha Malepati 26:10

Yeah, one of the things that I think can be really frustrating in this space as parents are navigating this is the idea that there is so much knowledge out there, and it's all being shared very anecdotally. There is no centralized repository for all of this information to live on. So, if you contact Terry, he'll send you all the stuff you want. I can call anyone in the rare-disease community, and everyone's so open and willing to share this information and these lessons learned. But we have not developed the knowledge infrastructure to share this information in a way that hopefully will end up being able to develop AI agents and all of these things to make this process much more consumable and digestible and applicable for specific families. But everyone has learned so much along the way, including very down to the specifics of what tox FDA accepted for my program to what endpoints we're using in our clinical trial and the issues we're running into. But we need to actually gather that information in a way that isn't just requires Terry to get on the phone with me.

Sylvie Raver 27:15

It sounds dizzying.

Sunitha Malepati 27:16

Yeah.

Ethan Perlstein 27:16

Terry's a busy guy.

Sylvie Raver 27:17

Exactly. Yeah. Like a Slack, a WhatsApp, phone calls, running your own platform.

Sunitha Malepati 27:20

So, that's one of the things we're trying to build out now, is just building out that hub of knowledge that is going to be curated and be able to be accessible to patient groups that are navigating this for the first time.

Sylvie Raver 27:32

So, it's like vouching of the trusted partners and elevating that to people to tap into. Incredible. So, it makes it repeatable.

Sunitha Malepati 27:38

Exactly.

Sylvie Raver 27:39

Okay. Maybe back to Terry. Across the science and the manufacture—everyone keeps pointing to you. I'm sorry.

Terry Pirovolakis 27:47

No problem.

Sylvie Raver 27:47

You're just really a pioneer here. What carries over from one disease to the next? What is repeatable? What must be rebuilt every time? Certainly, there are some elements that do still need to be bespoke, but can you talk a little bit about how you've maybe done that yourself or advised others?

Terry Pirovolakis 28:03

Yeah. I think as long as you remain a copycat, then you can copy from other people. But if you end up doing things that never have been done before, like if you're using a new capsid or stuff like that, that's when you're in a new frontier, and it becomes very complicated. I think in those instances, unless you have a really good plan and a really good team, you're going to run into a lot of issues and a lot of funding because the FDA is not going to give you leniency on new programs. They're going to want to make sure that it's safe and effective. So, what I say is, if—for us, when we started our program, we did a tox study in rats. It failed. Then we had to do a tox study in nonhuman primates. And we published all that on our website so people can use it and leverage it on their application. So, we share everything, and the goal is that you don't have to repeat that. But the reality is the FDA views that each program is individualized, and that you need to do the same steps to show efficacy and safety regardless of your disease or your pipeline approach. So, in the end, you still have to do them all. You may not have to do, for example, comparability studies in your product or stability studies in the tubing, in the vialing that you're using to say that it's stable 24 hours later, after you don't administer it. For example, we have four programs, and we have some times where you go to inject a drug and you can't get the right spot intrathecally, and that patient has now been poked three or four times. And we're like, "Stop." Like, "Let this patient go. Go home for a couple of days, come back, and we'll try again." In that case, you're supposed to throw away the drug after four hours. But if you do the proper stability study on that product line, you can say, "Well, put it in the fridge for 48 hours or 24 hours or two weeks, come back and we'll reuse it again, not throw away a quarter of a million dollars or a million dollars of drug product." The other thing we've also been very

successful at is families have been coming to me and saying, “I need help.” So, we publish all of our documents, and then we decided that we were going to do more, so we created a consulting division of Elpida Therapeutics. And the goal is to help families go from proof of concept to first-in-human, and we were fortunate enough to have two INDs filed this year. And then we went even further, and we realized that you need to own your own database. You need to own your own TMF. You have to own all the infrastructure, at least from the core documents. Otherwise, you’re going to beg institutions for it, and they’re going to give it to you half-assed, right? So, you have to basically own all that stuff. So, we became our own mini CRO. We have our own medical monitoring team, and so everything is in-house because we didn’t want to spend that money, and we didn’t want to rely on anybody else doing that for us.

Sylvie Raver 30:38

That’s incredible.

Terry Pirovolakis 30:38

You don’t have to go down that path, but you do need to have certain pieces of that puzzle, for sure.

Sylvie Raver 30:44

Takes a lot of infrastructure, which usually means it takes a lot of funding. Let’s talk about funding. Maybe I’ll go to Ethan. You mentioned the priority review voucher. Can you share—I assume this is a pretty knowledgeable audience, who are all chanting it back to you—but tell us a little bit about how the sale of that has been able to work with other types of investment capital. Where does each approach work best? Where could they work together? Maybe expand on the funding vehicles a bit.

Ethan Perlstein 31:09

Yeah. So, if you want to learn more about the PRV, go check out PRV Watch. It’s a great site made by a guy who’s just, in his spare time, collecting all the data about the sales and so forth. So, this program was started over 10 years ago. It’s been through some breathless renewals and some suspended activity for a while, but the core of the idea, again, is a market incentive created by the government that essentially facilitates a voluntary wealth transfer from big pharma to baby biotech. And it couples the insatiable appetite for new blockbusters that are coming out of big pharma’s pipeline with the development of rare-disease medicines for kids coming from small commercial sponsors. So, you don’t have to force pharma to care about rare. They can continue to just care about the biggest TAM, and that is the driving force that makes these PRVs valuable. Because instead of a 10-month review time, you shave off four months, and that four months of extra market exclusivity has a value. And a few years ago, it was valued at $100 million. About a year ago, it was about creeping up to $150 million. In the last couple of months, in fact, 2026 was a bonanza year. Record number of PRV issuances, record number of transactions, and the price keeps going up. It’s now above a $200 million floor. It’s pretty crazy. It’s doubled in a few years. The peak value was in 20—I believe—’14, ’15, ’16, when the program debuted, and the value of the PRVs peaked at about $350 million. Will it go back to that level? Who knows? Will it dip back down to $100 million? I don’t know. Sometimes it behaves like a cryptocurrency. But the point is, this mechanism hopefully is not going anywhere, and if the lame-duck Congress is listening, there is the Priority for Pediatric Cures Act, which was introduced by Gus Bilirakis last month, and you guys have weeks to sit around and, I don’t know, pass a budget, but maybe they can also extend this program forever because that is what keeps a lot of investors on the sidelines is, “Oh, what about the PRV expiring?” But we say, “Look, the clock is

ticking. You got three years right now. Right now, you got a statutory three years." And in rare diseases, three years is an eternity. I know that's nothing for big pharma, but in the hands of these operators, three years is an eternity. So, the hope is that the PRV will remain in place, and again, you don't have to change pharma. They can do what they want. They can feast on their big diseases, and at the same time, they can pull up hundreds, hopefully, over the next 10 years, hundreds or more of new rare-disease medicines for kids that had none before.

Sylvie Raver 33:33

Incredible. Your peers are in the room. I want to encourage participation. The QR code should flash up. Just a reminder that you're welcome to submit questions, and I'll take them on the iPad. I'd like to continue that thread with you, Sunitha. Your initiative blends—you talked about this a little bit in your opening and how you've thought about all these different types of capital. Let's talk about financing, blending philanthropic investment capital, sharing these playbooks openly. Where does each approach work best? How do you think about what Ethan has just shared?

Sunitha Malepati 34:02

Yeah. So, one of the things that is, I think, really frustrating, and I think I've heard Ethan say this before. Sometimes it's really crude, but people are just waiting for a wealthy individual's kid to get diagnosed with one of these diseases, and that can't be the basis for how we develop treatments for these conditions. And so, there's this huge equity issue that is involved in all of the work that patient groups are doing and how they fundraise. And I just believe that if people understood—philanthropy understood, impact investors understood—the opportunity in this space in terms of the impact that they can have, the lives that they can save and improve, that there could be a pooled vehicle that we could build out to take stock of this capital. I think if you talk to philanthropists, unless you know someone directly impacted by a specific rare disease, this is a whole black box. No one thinks about rare disease in the philanthropic space. They're thinking about education and climate change and all of these other big societal issues, and we have a huge PR problem in this space, where we don't understand how many people this actually impacts, and the implications for investing in this for more common diseases until you get diagnosed with this. And so, what we're trying to do is take a page from other sectors and do exactly what they've done, which is use philanthropic capital to de-risk impact investment or traditional private investment from coming in and take that cut. If there is a loss on the portfolio, just like there would be in any sort of VC-backed portfolio financing mechanism, that you've got philanthropic capital to backstop that in the form of a loan loss reserve. There are all these other funding mechanisms like PRIs at private foundations that can be used like loans. And what we really need to be doing is building out these blended finance vehicles to act in place of where the traditional markets are not working. That is the model that we are building out, and it's really not a novel model. It's just novel to rare. And so, we're talking to a lot of different funders about this. I think the hesitancy that we're hearing, the feedback we're hearing from the marketplace so far is, can patients actually do this? Can patient groups actually do this work? I'd rather invest in a biotech company than this. And I think what we're trying to argue here is that patient groups are doing this, and we've started to collect the data. At Buffalo Initiative, we have 60 different programs, and it really wasn't hard to collect this data very quickly, and I know there are hundreds and hundreds more. Sixty programs right now that are being parent- or patient-led in the neurogenetic space that could use this financing to drive science, where right now they're not really eligible for any other funding but from bake sales and lemonade stands, and we can't do drug development in that way. And so, we're trying to build out sort of this scalable, systemic way to pool funding in a new way.

Sylvie Raver 37:05

Thank you for explaining that. You mentioned a PR problem, and we talked about capital being so critical to this, but capital can also look like awareness and relationships and sort of the networks that pull things forward. Mitzi, this really speaks to what you've built with Countdown. Can you talk a little bit about how the network that you already maybe had established and how that's been impactful for your organization? What are some ways that other people could use your model, be repeatable, and build awareness through their own efforts?

Mitzi Solomon 37:37

I first just wanted to go back and say leading with a sense of urgency also. Because all of us on stage lead with a sense of urgency, and now we need everyone else to feel that sense of urgency and join us. I think when it comes to rare disease or common disease, when it comes to primary mitochondrial disease, for example, one in every 5,000 or so people have a primary mitochondrial disease. And then everybody has a secondary mitochondrial disease or mitochondrial dysfunction because we're all aging. So, we're all really in this together. But as far as PR and what we do at Countdown, when we started Countdown, my first goal was to really, again, I said, introduce the word mitochondria, and it's not a scary word. It's not a word that we should be thinking, again, only in the textbook or only when it comes to rare disease. Really recognizing that it really is everything, and to accelerate mitochondrial science and medicine, and to bring cellular energy into the forefront of human health. We really need to understand that it sustains life, and it has to do with everything that we do on a day-to-day basis. Recognizing what mitochondrial function does, recognizing that it has to do with our environment, how we live our lives, physical stress, emotional stress, nutrition. A lot of things in our life really affect our cells, but people don't recognize that connection. So, that's where we started. And then we built on that, and we built out six pillars because I also knew that philanthropy is very personal. And so, usually if it doesn't affect you, you don't really recognize that as something that you want to care about or that you want to fund. So, we decided to build out six pillars all around a mitochondrial lens. So, from prevention and precision diagnostics to chronic disease and aging, primary mitochondrial disease and rare genetic disease, women's health and hormonal longevity, because for so long women—studies weren't even being done on women. AI and frontier therapeutics. And then did I miss any? I don't even remember.

Sylvie Raver 39:43

I think that was five.

Mitzi Solomon 39:44

Yeah, that was five. Oh, what's my sixth? Oh, and mental health, brain energy, and cognitive resilience. So, basically covering all areas, and like I said, all areas overlap, but also wanting people to recognize that they can see themselves in our vision, and they can see themselves in our mission, and recognize that we can do all the work that they need to get done, but through that mitochondrial lens. For so long, people have been wondering, "There's no treatment for me. There's no cure. Doctors don't understand." And now we're giving them a way. So, a lot of the projects that we funded really are all high-risk, high-reward projects. And we want to see everything we do go to translation quickly, reach human application fast. Not just in our lifetime, but within the next three to five years. So, that's the kind of science that we're really doing, and we're really moving quickly, but responsibly.

Sylvie Raver 40:33

Incredible. We've got some audience questions, and I'll take them in the order—they're all great, but I'll take them in the order that they came in. I think this one's probably for Ethan, but anyone can jump in. The PRV is incredible, but what other incentives can Congress implement to de-risk and encourage more investment, especially for ultra-rare diseases?

Ethan Perlstein 40:49

Emil Kakkis talks about an ultra-orphan drug act and maybe carving out a different regulatory path for—I don't know what that magic number is—but fewer than 1,000—

Terry Pirovolakis 41:00

1,000, 2,000, something for non-commercially.

Ethan Perlstein 41:00

Yeah. So, I guess there's that, but if Congress can't pass a budget, I don't know what hope there is for something more complicated. Sorry, what was the other part?

Sylvie Raver 41:13

Anybody can take it.

Terry Pirovolakis 41:14

Yeah. I went to China a few months ago, and they were doing IIT pathways in Singapore and in Shanghai and—sorry, in Tokyo, in Japan. Other places are doing conditional pathway approvals, where basically, if you show kind of this meaningful path of efficacy, or at least a little bit of efficacy, you can then get a conditional pathway so the insurers start paying for the drug product while you do the remaining items to get to the full pathway approval. I think we need something like that or some mechanism where we go from treating a few patients, let's say eight or nine patients, and then that's kind of the end because you can't afford to make more drug product and treat more patients and continue that pathway to show that it's actually working. Because in a disease where children die within two or three years, it's fairly easy to show the therapy works. But in a disease like my son's, where it's going to take two or three decades, children don't have that time.

Ethan Perlstein 42:09

Yeah. If I could just add, I don't think Congress needs to pass anything else. Let me go back to our favorite three letters, PRV. I think the problem is not in Congress, it's in the culture, where people don't believe that parents can do this. And I don't know how many times they need to see an example. I don't know if we have to clone Terry. But we have plenty of others who are non-genetically related who have the same intention, and I just don't know why they're still invisible. But if people were to open their eyes and just believe what their eyes are showing them, these founder parents are here. We don't need any other magic mechanisms. And again, Congress can't even get its act together to pass a budget. How are we expecting it to—the laws are in place, the people are there, we just need to connect the dots.

Terry Pirovolakis 42:51

Yeah.

Sylvie Raver 42:53

Well, actually, segue to my next question a little bit. You're all incredible experts in citizen science and continue to improve what you're doing to supplement the ecosystem. But it's so frustrating to continue to supplement it rather than seeing the urgent change from the inside. What do you want to see the scientific community do to pull citizen science, your values, and models into their research? So, let's talk about what others than Congress can do. Yeah.

Terry Pirovolakis 43:18

I mean, the reality is there's a lot of great technology that's out there right now, like the CapX and the transferrin receptor vectors and next-generation programs that are available. It's just that we need industry to fund those to get them into the clinic so that we can then copy them and move them forward. And I think without real funding, we're not going to be able to do that. And funding is not going to come from families and parents; it has to come from large investments. And I think right now we are in an Arctic winter when it comes to biotech, and that has to change. And I think the government has to come in and start really funding these items. Think about how much we spent on the war. We could have spent a lot of money on innovative technologies.

Sylvie Raver 44:01

It's all about what you prioritize. You want to take any of that, too?

Sunitha Malepati 44:04

Yeah, I'll just say, I think that typically the way research is being done in academic institutions is it's curiosity-based science, which is really important. But we don't spend enough time, energy, investment in translational science, right? So, 10,000-plus rare diseases, 6,000 of them have a known genetic or molecular cause. We have scientific tools to actually correct these issues. And when you look at the pharma, biopharma pipelines, like 2 percent of those diseases are actually being worked on in that space. And so, you're going to have to be reliant on academic institutions and patient groups to actually do the translation. But there is no funding for that translation because NIH does not provide, but for a small fraction of the budget and through NCATS, any funding for translational science. Most philanthropists also only invest in basic science. And so, how are we going to actually take this incredible investment we've made as a society into these tools and apply them to diseases that are solvable today, unless we come up with new funding mechanisms to translate and more incentive for scientists to translate? It may not look great in a published paper. It may not show up in your tenure-track package. But we need scientists who are willing to actually make a difference for humans, not just mice and animal models. And that's really what patients are focused on.

Sylvie Raver 45:31

I concur. And it sounds like you all concur with that, too. Mitzi, this was directed to you, but I think anybody can actually speak to it. And it kind of expands on what you're just saying. So, maybe I'll go to the

other side of the panel. How the patient voice has shaped your organization's advocacy for what science gets funded. It really comes down to what is incentivized, and sometimes that incentive comes from the funding, sometimes that incentive comes from the advocacy and the very vocal and consistent voices from outside groups.

Mitzi Solomon 46:02

I mean, we're trying to unify a field that's been overlooked and underfunded for way too long. So, for us, we're kind of still in the Wild Wild West. I mean, figuring out what to do, where to go, kind of making up the rules as we go when it comes to mitochondrial science and medicine. For us, we started also recently Countdown Ventures because we recognize that there's a lot of for-profit opportunities with impact investing. There's also opportunities with venture philanthropy. And with this sort of field, when we're ushering in a new era of health, it's exciting to be on the forefront of that and for people to get ahead of that. Anytime you want to fund something, and you start talking about anything when it comes to, "I have a project and I know that this is going to move the needle," again, it keeps going back: we first have to educate, because when it comes to mitochondrial science and medicine, most people don't really understand it. But for us, it's really been a lot of family, friends. Now we're moving into the venture space. We're starting to get start-up companies that really want to get involved with our organization and start building with us. But when it comes to advocacy, like you said, it's also where the way that we've been treating a disease and the way that we've been looking at disease for so long just needs to change. We need to rewrite that narrative. And I also believe that it starts with the medical schools. They're so focused heavily on anatomy, and they're not talking about mitochondrial biology. And if they are, it's probably in a paragraph of the entire medical textbook. And then from there, there's nothing on the medical boards. So, as soon as they get into practice, they have no idea when they look at a newborn baby or they look at a four-year-old and they say, "Well, don't worry, they'll catch up," or, "Well, let me send you off to someone else." They have no idea about mitochondrial dysfunction, anything to do with treating and looking through a mitochondrial lens. So, I think it's kind of all of the above, but I think once people start to really understand where the science is heading, people will start backing more projects in mitochondrial science and medicine.

Sylvie Raver 48:07

Thank you. This is a good one. Experimental treatments don't always succeed as hoped. How do you maintain momentum and manage concerns when many of the genetic tools, in particular in this space, can be so challenging? How do you maintain that perseverance and the momentum when things don't quite go maybe the way you've expected? Who wants to start?

Terry Pirovolakis 48:25

Yeah. When I was trying to make Michael's treatment, I had this vision that we were in the operating room, and I was doing a prayer for Michael. And every kind of setback that we had always led to that vision, right, of him being in there. And my new vision is that we're going to get this approved, and that's kind of how we go forward. And there's a lot of problems that happen along the way. Trust me, I know. But if you continue moving forward and not look back and not blame people and take responsibility and do the things that you're supposed to do as a leader, then you move forward. Going back and arguing about what happened yesterday is not helpful, right? The only thing I do is move forward. Move forward. That's continuously moving forward. That's what I would say.

Ethan Perlstein 49:06

I mean, that's the attribute of every entrepreneur, is that they don't—failure's not an option. And if it's your kid, it's even times two, times a million. So, it's almost like the people that I know, that question doesn't even come up because it's just, "I have no choice."

Sylvie Raver 49:25

Well, we're nearing the end. I want to move to some closing remarks, and someone who submitted a question read my mind. So, I'll kind of end with this, give you each a couple of minutes to expand on this. What's the most impactful thing? What is one big takeaway? We've heard a lot of repetition of reinforcement of what we're doing and what needs to come next and what some of the systemic barriers are. But if you were to distill it, one thing that a patient advocacy group or a parent or someone in this room should really take away from this conversation. I can go down the line.

Sunitha Malepati 49:56

Gosh.

Sylvie Raver 49:56

Oh, no, I'm starting with you. I'm so sorry. I can come back to you if you want?

Sunitha Malepati 50:01

Yeah. I think, sort of going back to the topic of this panel, right? I think initially when you're in the health-care system and going through this journey as a parent trying to figure out what's going on with your child, you feel beholden to all of these other people. And you feel like, "I don't know anything. There are experts in the room that are going to tell me what's going on with my kid." And we were failed so many times. We went to so many experts up and down the East Coast. We finally got an answer, but that was like they felt like they checked the box of, "We did our job, and now go live your life." And what I realized is none of this is going to change on its own unless you take a leadership role and you demand a seat at the table—a leadership, not at the end of the table, but as the central part of the table. Or build the table yourself because there are actually a lot of people out in this space that want to help you and that will help you. But it's going to require you taking a leadership role and not to feel like you can't make a difference in this space. Because what we're seeing every single day is new therapies coming online because a parent or a patient or a community stepped up to the table when no one else would.

Sylvie Raver 51:14

Thank you. Ethan?

Ethan Perlstein 51:15

I mean, the science is not limiting. The talent is not limiting. God knows the diseases aren't limiting. The only limiting reagent in this equation is capital. And if I get introduced to a new family, genetic lightning strikes, they start their odyssey. I dispense with all the usual pleasantries and just cut to the chase, which is like, "You're going to need money." And I know that sucks, but that's step one. The science is really hard,

but that first step is the fundraising, which is sometimes insurmountable, it feels. But you have to go in there with eyes wide open, knowing that everything else is ready, but you do need the capital.

Terry Pirovolakis 51:53

For me, two things. One is, when you're a parent, you get diagnosed, no one's coming to save you. People want to help you. Picture it's like you're having your neighbor come over for a party, right? Well, they can leave at any time, but you can't, right? So, you can't leave your own house. So, my thing is, no one's coming to save you, and you have to be all in. If you're not all in, and you're like, "Oh, on a Saturday night, how am I going to raise money sitting on the couch?" It ain't going to happen. For me, Saturday nights were going to clubs and handing out donuts to drunk people to raise money. That's how we were doing on Saturday nights.

Ethan Perlstein 52:28

Why didn't you invite me?

Sylvie Raver 52:29

Unorthodox, yeah.

Terry Pirovolakis 52:30

You know? The thing I think we need to do most, the most important thing right now for us to do is go back 20, 30, 40 years and think about what advocacy was, right? Advocacy was locking yourself to a building, hardcore philanthropy. And what we're doing now is we're talking about things. We're not going to move forward, and we have a huge opportunity. There's 10,000 rare diseases. Forty million Americans. If we really stepped up and said, "Let's get out of our way. Let's take the we all hate each other kind of thing and come together and say we want real change." If we did that, if we came together and we all had one voice, we could really make a true impact. And by doing it individually, and one person going to newborn screening, the other person doing this and that, we're not achieving the goals we need to achieve. And we have to come together as one group, one voice, and say, "This is unacceptable." We need real funding. We need real support. We need really to do this, or else we're never going to get there. And that might mean locking ourselves at the entrance of the FDA or Congress and saying, "We're not going to move." But we have to do it, not one person. It has to be thousands of us.

Sylvie Raver 53:40

At least four.

Terry Pirovolakis 53:41

Tens of thousands. Yeah, exactly. Maybe we'll do that tonight, who knows?

[Laughter]

Sylvie Raver 53:45

That's a Friday-night activity, not a Saturday-night activity. Mitzi?

Mitzi Solomon 53:52

I agree with everything they said. Obviously, we need funding and we need lots of it. I never feel bad or feel guilty or I never not ask. That's my job now. It's to ask so that I can be a better parent, I can be a better advocate for others. Everyone deserves to be treated equally and also recognize that we shouldn't always have to be the CEO of our own health, but yet now we do because if we're not, who else is going to advocate for us? As a parent, I recognize that I look at my children, and you see that they need you, and so now they're needing me in this role. So, as a leader, I also ask others to join me and to really help be with me on this journey. I also know that I'm not the smartest person in the room, so I want to surround myself with people that are even smarter. I want to surround myself with scientists that are not just the scientists that have been there doing the same work 10, 20, 30, 40, 50 years, but also these up-and-coming scientists who have this incredible science and this incredible gift of entering this new age of health, and we need to be able to fund them as well. Again, the projects that we choose, I really choose projects that are wow projects. I really don't want to see things sitting in a lab. I want to see things making impact and making impact fast. One of the projects that we just are working on now with Dr. Jim McCully at Harvard and Boston Children's is the first mitochondrial transplantation for Duchenne muscular dystrophy. And we decided to start with Duchenne muscular dystrophy because it's the hardest case. So, where else would you start but the hardest case? So, then you're able to move forward and do other things from there. So, I think, of course, funding is number one, and for people to understand the science that we are working on. But two, it's also coming together and recognizing that we can't do it alone. And so, all these voices on stage are a lot louder than one.

Sylvie Raver 55:47

Well, what a good note to end on. We've covered tenacity, we've covered urgency, we've covered creativity, advocacy, donuts *[Laughter]*, places that we didn't even expect to go. Thank you so much for being here. Thank you for being here. Thank you for sharing your time and talent. Lots more to do ahead.

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