

## Science Will Win S1E3

**Emily:** When my son was diagnosed with Duchenne and we set up the charity, I remember meeting a mom who said, well, you know, it's all very well you doing all this work but you do realize that these drugs are not going to be reimbursed by healthcare payers. And I looked at her with incredulity and I said, don't be so ridiculous. My son has Duchenne muscular dystrophy. How could they not pay for a treatment?

**Adam:** That is Emily Crossley. You might remember her from our last episode. She is the co-founder of the charity Duchenne UK.

In 2014 Emily came to understand what that mom was talking about. That year, a drug to treat Duchenne was given conditional approval in the UK, but it took years to figure out how to pay for it and actually make it available to eligible patients.

**Emily:** And in that time, we have parents who were celebrating in 2014 because they finally found a drug that had been approved only to find that in the two years that it took to make a decision, their sons became ineligible for that drug because one of the conditions of the drug was that you had to be ambulant. You have to be walking to take it. So in 2014, their sons were walking and they celebrated. By 2016, their sons would stop walking. And I realized in that moment that there was something far worse than having no approved treatment for your condition. And that is having a treatment that has been approved for use but it's sitting on a shelf and you can't get to it because no one has worked out how to pay for it.

**Adam:** And this is one of the biggest challenges facing everyone involved in providing healthcare - especially when it comes to assessing the potential value of innovative medicines, like gene therapy, where there are still so many unknowns.

This is episode 3 of Science Will Win, a miniseries about gene therapy. I'm Adam Rutherford.

Now, just a reminder before we get started - gene therapy is a promising area but it's investigational in nature for many diseases. There is much research still to be done to better understand the safety and efficacy of these potential therapies. Remember, you should always discuss treatment options with your healthcare provider.

This week, we're taking a look at the healthcare ecosystem gene therapy is entering. What does it look like in terms of policies, regulations, infrastructure? These are all the things that need to be put into place to ensure that eligible patients will have access to approved gene therapies if they choose to pursue them.

Genetic rare diseases affect people all over the world. Many countries are starting to prepare for the advent of gene therapies and looking at how they can solve for some of the big challenges ahead. In this episode, we'll be looking at the U.S. and Europe as examples.

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First, let's hear from someone about what's happening in the U.S.

**Bert:** I'm Bert Bruce. I am the regional president for north America here at Pfizer in our rare disease group.

**Adam:** Bert has worked in the pharmaceutical industry for his entire career. His dad also worked in pharma, and his mom was a nurse. So for much of his life, he's seen the power of medicine to help people in need.

**Bert:** I didn't seek out rare disease, but I did seek out the industry and that's what keeps me here. The ability to help greater and greater numbers of people be able to live their fullest lives. That's a pretty big gift.

**Adam:** Bert has also watched as gene therapy development has faced hurdles as policy makers struggle to keep pace with innovation.

**Bert:** A policy is set to be able to give guidance as to how to be able to utilize something. What you're talking about is something that's not been done before. There's an inability to use any precedent to be able to help you understand how to actually meet the societal goals that you're trying to achieve. I mean, sort of, a rough analogy, maybe what we're seeing actually in the world of vaccines, right? So you've had a global pandemic which you've never had before, but there was a tool that's available.

**Adam:** That tool was the Emergency Use Authorization.

It's set up for life-threatening or emergency situations, in which there is no other treatment or preventative measure available. In those circumstances, regulators like the U.S. Food and Drug Administration can offer expedited authorization for medicines or vaccines that have not yet been fully approved. It's exactly the process that was used to authorize COVID-19 vaccines in 2020.

But the Emergency Use Authorization doesn't currently exist for something like gene therapy. A rare disease isn't classified as a public health emergency, even if the patient need is urgent.

**Bert:** The emergency authorization use it allows a framework to be able to be followed, something like that doesn't exist in gene therapy. So what you have to do, I believe, is understand the level of scientific differentiation, how different is this, and then what are the policies that need to be created and put in place before they arrive, not after they get here, but before they arrive. And why do I say that? Because if it's after they get here, then there's someone who has the ability to benefit and the time to give them that benefit is delayed. And that's the goal that we're all trying to reduce by creating policies and by creating regulations is to be able to get the access to the appropriate patient as quickly as possible.

**Adam:** And this isn't unique to the U.S. It's a sentiment we also heard from Professor Tomislav Sokol, a Member of European Parliament.

**MEP Sokol:** Yeah, that's always the problem law or regulation always lags behind. So you always have a new situation, develops a new issue in your topic, new problem, whatever. And then the legislation follows suit. So I do not think that we can resolve this problem by providing concrete regulatory solutions by kind of anticipating everything that will happen. But what is important is to create landscape, which is not too detrimental, too stiffening for private initiatives. So I think that is important. So it's not the regulators who have to think of all the future possibilities. But to actually create framework which stimulates others to actually look beyond the horizon.

**Adam:** These are just a few examples of how complex health care policy can be. Typically, policy is reacting to something. It's not predicting what might come down the pipe. And that's where speed and urgency can break down.

**Erik:** Science has really leapt forward in this new frontier of medicine, but unfortunately the healthcare system has not kept up with the science.

**Adam:** That's Erik Paulsen. He was in our last episode - former U.S. Congressman, currently the chairman of the Institute for Gene Therapies. We're going to hear a bit more from him a little bit later. As we've talked about already, just getting to the approval process for gene therapy starts with many, many years of previous scientific work and testing.

In the U.S., review and potential approval by the FDA requires a lot of steps. And that's important. Drugs need to be rigorously tested. Even in addition to the three phases of clinical trials, there are applications, labeling reviews, facility inspections. And then, if it all passes muster, a drug or treatment makes it to the final approval. At that point, there's still monitoring and collecting of real-world data.

Now this approval process in the EU is very similar.

Now strap in here, cos we're getting into the nuts and bolts of getting a therapy all the way to a patient.

If a drug is approved by the European Medicines Agency, it's authorized for use in all 27 member countries at once. However, before it can actually be available to patients in any given EU country, they're each going to need to figure out price and reimbursements between payers and manufacturers. This is generally called 'value assessment'. And it depends on a lot of data about a number of factors: safety, efficacy, how innovative it is, how durable, or long-lasting it is, how many people could be treated, and the financial impact to health systems and patients.

With all these variables, it can get rather complicated.

And it's especially difficult for gene therapies because it's challenging to provide the gold standard of data – which is long-term clinical evidence across large patient populations. Remember, these are rare diseases we're talking about.

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**Karolina:** So there are many challenges then that the gene therapies, face and especially patients are facing in terms of accessing the treatments. I would probably start by the issue of health technology assessments as this is the issue that was raised and is raised by many manufacturers of advanced therapies. And where also patients have also a voice. So in Europe, we have the health technology processes that are done at the national level.

**Adam:** That's Karolina Hanslik. Karolina was involved with the Rare Impact Project at EURORDIS, the European Organization for Rare Diseases.

Health Technology Assessment, or HTA is the process used to inform healthcare decisions for new technologies. It looks at a new drug or therapy and measures the added value when compared to the treatments we already have. They do this by analyzing clinical trial data. But when it comes to gene therapy, those clinical trials look different, and that could affect how gene therapy is valued, or it could mean that a country decides not to pay for this new treatment.

There are some signs that the HTA process is changing. Just this summer, the EU signed a provisional agreement that would create joint HTA reviews across EU countries. It will go into effect in 2024. The intention is that this would streamline the decision-making process, to foster faster, more equitable access to medicines for patients across Europe.

Though it should be said, some are concerned this new provisional agreement could lead to even more complexity.

Another challenge of working within the European Union comes up with cross-border health care.

**Karolina:** There are some small countries in Europe that probably will have to send the patients abroad, for the highly specialized treatments. So in a way, we need a collaboration between the members states in order to give the possibility and the authorization to the patients to get the treatment abroad.

**Adam:** OK, let's take a moment to think about what this means. Let's say you have a rare disease. You live in a small country in the EU. And you have great doctors, but they don't specialize in treating your specific rare disease. But there's another, larger country where there are doctors with that expertise. You're going to want to travel there to get access to that talent.

But, of course, it's not that simple. Let's go back to Professor Tomislav Sokol, the Member of European Parliament. He's also a professor of health law at the Catholic University of Croatia. And he's been involved in a lot of these policy conversations in the EU.

**MEP Sokol:** So if you are a patient, it's extremely complex for you to access the best possible health care in the European Union.

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**Adam:** That's because, as Professor Sokol explained, there are different national regulatory systems and different regulatory and ethical rules. Plus, data sharing across different EU member states is also a challenge.

And to top it all off...

**MEP Sokol:** We actually have two sets of EU rules, which regulate the same issue, cross-border healthcare directive and regulations of social security coordination, and these rules are similar, but they are still containing important differences in terms of conditions for actually getting health care abroad and the amount that will be in the end reimbursed.

**Adam:** So there's not just one solution to all of this. In some cases, it's going to mean a change in the way these systems are designed. But there are some intriguing ideas for collaboration. Stay tuned, we're going to get into those in our next episode.

For now, let's travel back over to the U.S., and back to Bert Bruce. Because there's a similar cross-border healthcare challenge over there too.

**Bert:** So what you refer to as cross border movement is not fundamentally much different than driving from Texas to Florida. Because if you can get access in Florida, then I'm going to go to Florida. I'm going to go there, right? Because that's what, that's what families will do to be able to get access to healthcare.

**Adam:** Now what Bert is describing here is cross-state healthcare. People needing to travel from one part of the country to another to access the expertise and the care that they need.

Seems simple enough, it's all happening in the same country, after all. But it becomes tricky when it comes to how we pay for these treatments.

First, what you need to know is that the health care system in the U.S. is set up with private insurance companies, and two different government-funded programs: Medicare and Medicaid. In 2020, about one fifth of the U.S. population used Medicaid for their health insurance.

Now, Medicaid is funded by the federal government and the state government and different states will set their budgets based on their own needs, such as population numbers and demographics.

But that doesn't mean that it's any easier for someone to get where they need to go to access the best possible care. And this brings us on to the topic of treatment centers or centers of excellence.

**Bert:** So if we talk about Duchenne muscular dystrophy, and there are phenomenal treatment centers, we'll call them centers of excellence. They're not always, but often, affiliated with academic institutions. And so if you think about those large health systems, they also have access to all of the other ancillary

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elements of care that need to be provided both for patients with DMD and others. Now, the proximity to get to that center may be very different for somebody. In New York City maybe not so much, maybe in Illinois, depending on your proximity to large cities, but when a disease doesn't distribute by geographic distribution, or geographic intensity, then it doesn't matter what state you live in, if in order to get there it's a four-hour drive or a 10 hour drive.

The distance between where you can get great care and where you happen to live, how often that care is required, what is affected in the individual and are there other parts of the healthcare infrastructure, whether that be therapists, physical therapy, restorative therapy that you'd need to also be right. Those things hit different diseases disproportionately.

**Adam:** All of these variables become part of the question of value assessment in the U.S. The years and years of research and development. And the complexity of getting gene therapies to patients. Here's Erik Paulsen again.

**Erik:** The healthcare system today is really set up to treat acute care or chronic illness, and pain that someone might have if they go in to see the doctor. Right. And so it's sort of a treating the symptoms concept, treating the symptoms is very different than treating the root cause of a disease, for instance.

**Adam:** And gene therapy is creating an entirely different healthcare paradigm.

**Suneet:** All of our models are based on a continuous use. You know, I take out a prescription and I take a pill and I use it and then I get my prescription filled the next month. And I do it again and again, and maybe I do it for one year. Maybe I do it for 10 years.

**Adam:** That's Suneet Varma, global president of rare diseases at Pfizer. As he describes, gene therapy is different.

**Suneet:** It's almost like a surgery, right? Which you do once, but it's not a surgery. And we really are concerned about the durability of the product, which is once you're treated with gene therapy, you know, does the effect last five years, 10 years, 15 years, we're going to continue to follow up with these patients to monitor them over time. So that is also a new way of, partnering with healthcare systems, with doctors, with providers, coordinating the care and all the long-term follow up, all that has to be, considered.

**Adam:** The current payments and reimbursement system just isn't set up for something like gene therapy, which could have a large upfront cost as it's a potentially one-time treatment. And that affects all types of insurers in the U.S. – public and private alike.

**Erik:** Let's just say there's an employee at a company who has health insurance, and they're treated for a health condition. Their insurance pays for that treatment. But some of these new gene therapy treatments might be a very expensive treatment. And so the, the insurer, the private insurer may not

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want to pay for that treatment because it's so expensive. It impacts just one person at the company. And it could affect, you know, the rates for everyone else in the company.

**Adam:** And this is just one hypothetical example. But it shows just how important it is to support access for innovative gene therapies and better understand the potential value that gene therapy may provide. Here's Erik again.

**Erik:** So making sure that our federal systems are set up for value where there's risk taken by the healthcare providers, or industry, for instance, if there's no benefit to the patient, then that's the risk that those research dollars have gone into. But if there's benefit for the patient, that's where the federal reimbursement system needs to make sure it's reflecting that value.

**Adam:** How do we do that? Well, I asked Suneet about that, too:

**Suneet:** There's lots of new ways we can do it. And I think those new payment approaches, like spreading, which I call annuity payments. Like, Hey, instead of paying it over one year, why don't we spread the payments over five years? Okay. And it will match up with all the patient follow-up that we're doing anyway. What about outcomes-based arrangements, meaning look, we'll promise or guarantee that this will have a durable effect for four years, five years, six years. And if it doesn't then you pay less, right? These are the kinds of concepts that we're coming up with because we don't know, everything right now that we're studying will actually work exactly the way we hope, that's part of the discovery. That's part of the science. So we ultimately want to tie our reimbursement to how well our treatments and medicines work and how much they improve the patient health.

**Adam:** And this work means a lot to Suneet, professionally, but personally, too. He's a carrier of a rare genetic disease called beta thalassemia minor.

**Suneet:** We want to be radically patient centric. We want to have that intimacy and that relationship, but we are also in our unit, the patients themselves, and it's either us or our family members. So it becomes incredibly personal for us. And that is super motivating. And when you take that sort of high patient impact combined with what I think is some of the most pioneering science going on in the world, in gene therapy, this really is central to the innovation thesis of the life sciences industry. So it's an amazing time and place, and I'm just so you know, to be here. And I'm so fortunate to be a part of it.

**Adam:** Now, all of this may feel like it's in-the-weeds policy wonk stuff. But remember Emily Crossley's story from the beginning of this episode – the reason we're in these weeds is because we want to get approved treatments to the right patients. There are so many pieces of this puzzle we need to bring together to make gene therapy a real option for patients around the world for whom it is medically appropriate. And access is really a key word here.

It doesn't stop with Europe or the U.S., either. Because again, rare diseases can affect anyone, regardless of where they live. That is something that informs Nikhil Gadre's work.

**Nikhil:** So it is our fundamental desire to ensure that healthcare inequity is not the way of life moving forward. It's about how do we work and partner with governments, we partner with healthcare systems to raise the standard of healthcare treatment. Some of that involves drugs, but a lot of that involves the diagnosis and the infrastructure that needs to be built up in, in countries all over the world.

**Adam:** Nikhil is Pfizer's hemophilia gene therapy commercial lead. And he lives with a severe form of Hemophilia A. As a child, Nikhil grew up in India where he didn't have the same access to treatment as he does now in the U.S. And so he knows firsthand the importance of global access.

**Nikhil:** So we are very committed and I am very committed to ensure that as somebody who has come from an emerging market from a developing country, that I don't ever forget, that there are patients all over the world.

**Adam:** For many, the very first step to access comes with a diagnosis.

**Durhane:** The challenge for rare diseases is that each one of these diseases are small in numbers. In many, many cases, they're are lost in the cracks of the healthcare system, even in the very best healthcare systems. I mean, Canada has an amazing system. Many of the European countries have amazing systems. And quite frankly, because these diseases are not well-known, they don't get diagnosed. We get patients who seven, 12 years into, you know, before they get a diagnosis sometimes if you caught them early on, you could have prevented all kinds of symptoms and even death. We have real challenges in terms of their getting access to services.

**Adam:** That's Durhane Wong-Rieger, you might remember her from an earlier episode. She works with Rare Diseases International. Her children were both born with rare diseases, but they struggled to get diagnoses. And that's a common challenge in rare diseases.

**Durhane:** We find many diseases are not diagnosed until there's a treatment because clinicians don't know about it. Patients don't know about it, and it's not until there's actually treatment that certainly you do the education, you do the awareness and in some systems, which actually does make sense, the diseases will not be a diagnosis unless there was something that they call actionable.

**Adam:** So I just want to underline that – sometimes for a rare disease, a diagnosis may not even happen in the first place if a treatment isn't available. And that can have huge implications.

Just getting a diagnosis is important. But so is when you can get it.

**Katherine:** You know, what do newborn screening programs look like? Not only from a national policy priority perspective, right. But how does one actually implement them and get a health care system prepared for a newborn screening program? Do patients actually want to know in those newborn

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periods? Right. So I think there's also that policy preparation that is taking place and is a priority over the coming years.

**Adam:** That's Katherine Beaverson. She's Senior Director and Patient Advocacy lead at Pfizer's Rare Disease Research unit.

**Katherine:** There are many things that I love about it. And the promise of being able to impact these families that are really burdened by rare genetic diseases. I'm professionally trained as a genetic counselor. So I spent over 10 years in an academic hospital working with individuals and families as they made their way through the journey of a rare disease from trying to figure out what is going on, to that diagnosis, to understanding what are the immediate needs for care, not only for the individual, but for the family and then working through the decisions that need to be made around things like genetic testing around extended family members.

**Adam:** And so Katherine is really intimately involved in this process, talking to patients and their families.

Each year in the U.S., about four million babies are screened for serious disorders. And out of those four million, about 12,000 babies are diagnosed each year. Without that diagnosis, they can't get available treatments for that disease. But, as Katherine has seen firsthand, the knowledge is important, but it also comes with a new set of challenges.

**Katherine:** So while there's this relief and access to information and resources, there's also the onset of grief, right. Now, we have to figure out what are the expectations that I had for my child or myself, right. And marry that with a new reality. And that is a process of grieving.

I would like to emphasize that when families enter into this diagnosis, a challenge is giving up control. They are now in a situation that is out of their control. And I think human nature is we want to figure out what is the control that we can take back. And accessing that information and accessing the best care allows these families to assume some kind of control over their situation.

**Adam:** Getting a rare disease diagnosis can change everything. And finding that sense of control for families can feel more possible if there's an available gene therapy, or a gene therapy clinical trial.

Brenda Cooperstone has experienced this firsthand. She's the chief development officer for rare disease at Pfizer. And in her role, she is constantly talking to patients and their families. Sometimes in unexpected places.

**Brenda:** So I was getting my haircut, which I do, I will admit. And sitting in the salon, in the chair of the stylists that I know very well. And she knows that I work specifically in the field of rare diseases. So she tells me a story, about a woman that she knows who just had a baby a few days ago.

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**Adam:** The baby underwent a newborn screening. And the test came back positive.

**Brenda:** And she asked me if, have I ever heard of this disease called SMA or a spinal muscular atrophy. And it just so happens that I know it quite well because it's one of those diseases that is very rare and genetic and for which there is, at the time there was a brand new gene therapy.

**Adam:** In fact, that's why there was a newborn screen in the first place. Just a few months earlier, that diagnosis may not have been possible. And without a diagnosis or treatment, that baby, or others like him wouldn't have made it into childhood.

**Brenda:** And she asked to put that woman in touch with me, and we did have a great discussion about the options for her child.

**Adam:** And this made a huge difference in that child's life.

**Brenda:** This is a devastating disease. It's one in which many children don't live until their second year of life. And those that do are severely debilitated. And I can tell you with this family, I get pictures, I get videos. This little boy is now two, and he's just beautiful and growing wonderfully and is just now learning to walk. I will say that, it just, it makes my heart feel wonderful it's motivation for me to get up every morning and go to work knowing that there is the potential to have that kind of impact on a family and on a child.

**Adam:** So we've covered the broad strokes of how we got here and what's happening right now. In our final episode, we're going to be taking a look at the future of gene therapy. The impact it could have on patients' lives, our healthcare system, and beyond. And we'll look at some of the things we'll need to do in order to get there.

Science Will Win is hosted by me, Adam Rutherford.

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See you next time.