The Rare Disease Gazette

Conversations with the world's experts about rare disease

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ETHICS OF RARE DISEASE

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Editorial

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Rare Disease Detection: Rare But Not Alone

The plight of patients with rare diseases is a critical unmet need of patients in healthcare. The statistics are frightening; there are 7000 rare diseases in the world that affect 350,000,000 people. One in eleven Americans has a rare disease. Three-quarters of patients with rare diseases are children and only half of patients receive an accurate diagnosis. The average delay for a patient to receive a diagnosis with a rare disease is 1 1/2 years. It is deeply concerning that one in four patients with a rare disease waits four years for an accurate diagnosis. There is an urgent need to communicate knowledge and expertise in the field of rare disease detection.

The journal *Science*, (American Association for the Advancement of Science) in collaboration with Fondation Ipsen delivers international science webinars for the general public.

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

James Levine

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The Conversation

Experts of the month: Erika Berg, Ph.D, hosts a conversation with world's experts about rare disease: The Ethics of Rare Disease: Balancing the Needs of the Few with the Needs of the Many

The Conversation

Experts of the month

Annie Kennedy
(EveryLife Foundation for Rare Diseases, Washington, DC)
Ulf Persson, Ph.D.
(Swedish Institute for Health Economics (IHE), Lund, Sweden)
Hadley Stevens Smith, M.D.
(Harvard Medical School, Massachusetts, USA)
Mark Trusheim, M.S.
(Tufts Medical Center, Massachusetts, USA)

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

"We continue to have a real barrier, not just with the uptake of rapid whole genome sequencing, but also with the uptake of newborn screening and other diagnostic testing across rare disease in general, is that providers, especially pediatric providers, are trained to look away from suspecting rare diseases when they are considering a diagnosis."

– Annie Kennedy

Erica Berg (host):
The ethical challenges surrounding rare diseases sit at the crossroads of compassion, innovation, and equity. How do we, as healthcare systems, policymakers, and as a society, balance the urgent needs of individuals living with rare conditions against the broader priorities of public health? Today, with a brilliant panel, we will explore the growing impact of patient-led evidence and advocacy in shaping fair systems of care. We will look at how global economic frameworks influence reimbursement and access to rare disease treatments. We will also consider the ethical questions tied to genomic testing, fairness and the family experience. Ultimately, our goal is to shed light on how societies can strive for both equity and efficiency in addressing rare diseases so that progress for the few can ultimately benefit the many. I would now like to take the opportunity to welcome our excellent panel. I will give each of them a chance to say hello and introduce themselves.

Annie Kennedy:
My name is Annie Kennedy. I am the Chief of Policy, Advocacy and Patient Engagement for the EveryLife Foundation for Rare Diseases. We are an evidence-based policy and advocacy organization that represents our broad rare disease community here in the U.S.

Hadley Stevens Smith:
I am an Assistant Professor of population medicine at Harvard Medical School and Harvard Pilgrim Health Care Institute. I am also a faculty member of the Harvard Medical School Center for Bioethics. My research program evaluates the clinical, patient-centered and economic impacts of genomic medicine interventions. Much of my research has focused on evaluating the use of genomic sequencing to screen for and to diagnose rare conditions for newborn and pediatric patient populations. I have been particularly interested in advancing the methods that are used to capture the impact of genomic sequencing and rare disease diagnoses for children and their families.

Mark Trusheim:
I am the Strategic Director of NEWDIGS at Tufts Medical Center, where since 2010 we have been running multi-stakeholder consortiums addressing the challenges of rare disease. Back then, we began with the regulatory challenges of how to deal with very small populations compared to the classic large population drugs and conditions. Then in 2017, we shifted to include the downstream market access needs for payment and reimbursement, particularly for cell and gene therapies, but also for the range of rare disease therapies. So, we have been at this for about 15 years or more.

Ulf Persson:
I am a health economist and nowadays I am a senior advisor at the Swedish Institute for Health Economics. I have also been involved in building the Swedish Reimbursement Authority for Pharmaceuticals. As a member of the board, I had a lot of experience with the challenges of getting new orphan drugs into the reimbursement scheme.

Erica Berg (host):
Mark, how high would you say are the structural barriers for medical innovation in the rare disease space compared to more common medical conditions, such as cancer, and to what extent have you seen this barrier be lowered in recent years, if you have indeed seen that?

Mark Trusheim:
I think rare diseases have experienced a striking paradox over the past decade or so. If you look at rare disease writ large, the barriers have been coming down. There has been an explosion of rare disease therapies approved over the last 10 or 15 years and there has been more research in that space. However, if you compare it to the need in the rare disease space, and if you are involved in any way in an individual rare disease, the barriers remain astonishingly high, both in terms of securing research funding and finding patients to help understand the mechanisms and natural history of these conditions. There is still a tremendous amount of work to be done compared to the larger conditions that have entire institutes at the NIH dedicated to them. It is very different for any individual rare disease to move forward. So, it is a tremendous paradox: on one hand, a great success; on the other, we still have thousands of diseases that re-

ceive no attention at all. If you suffer from one of those, you feel like you are starting from nothing, which in many cases, unfortunately, is rather true. The barriers are simultaneously extraordinarily high and, in some ways, far lower. We are seeing this now as an established approach and field in drug development, whereas 15 years ago that was not the case.

"One of the key concerns in the rare disease space is that most rare diseases remain hidden because we do not have a reliable way to see them in our datasets in our health systems."

Annie Kennedy:
I think Mark set that up really beautifully. Maybe I can just fill in with some statistics and context around why that is. Today, rare diseases affect approximately 30 million Americans in the U.S., and we understand that more than 50% of people diagnosed with rare diseases are of pediatric age when they are first diagnosed. We also know that the majority of those diseases are fairly rapidly progressing and that right now fewer than 5% of rare diseases have FDA-approved therapies. So, there is a significant unmet need and urgency. That really speaks to what Mark was saying, in that we still have a high threshold for need in the rare disease space. But perhaps we should talk about what those thresholds for entry into rare disease might be. Because I think we are going to dig into that and how those incentives have been established over time.

By nature of the definition, rare diseases have very small patient populations. Even in some of the more common rare diseases, as we learn more about those conditions, we learn about mutation specificity. So, we are learning about subpopulations within those populations. This adds to the complexity of designing clinical trials and studying those patient populations. In our rare communities, we have nascent natural history, and we are learning so much about the importance of having longitudinal data around our communities. We have significant diagnostic delays in rare disease. At the EveryLife Foundation we conducted a study about this, and we found that the mean diagnostic odyssey for rare disease patients is close to six years. That is a very conservative estimate. That means that from the time a parent or an individual first identified that there was a concern, it took over six years to get a diagnosis. We also know that this includes seeing 17 providers and making multiple out-of-state trips, which requires a coverage and reimbursement system that allows for that travel, and the ability for someone to afford that. We will explore those costs throughout this conversation.

We also have data that shows that it takes 15 years and over $2 billion to develop a therapy, and that most therapeutic concepts will never make it into the regulatory environment. Finally, once there is an FDA approval, there is a very complex access ecosystem that makes reimbursements for many of those therapies extremely difficult. So, those are all the complexities.

One of the key concerns in the rare disease space is that most rare diseases remain hidden because we do not have a reliable way to see them in our datasets in our health systems. We often use ICD codes, or the International Classification of Diseases, to identify rare diseases. While we estimate that there are more than 10,000 rare diseases, we have fewer than 1,000 ICD codes for rare diseases. As a result, even once a diagnosis is made, we are unable to track it, see it, identify it, or study it in a systematic way in our communities and across our health systems. There are so many hurdles and barriers, and while we are working hard to overcome them, we still have some massive challenges to face. That said, I am really grateful that we can have this conversation today to talk about what we have done to overcome many of those hurdles, and to even reach a point where we have approved therapies for 5% of rare diseases, and patients alive today, who ten, five, or even three years ago, would not have been.

Erica Berg (host):
Ulf, I am wondering, from your perspective, if you are seeing the same progress and the same lowering of barriers, and whether you are seeing anything different in the European ecosystem?

"In some countries, like in the United Kingdom and in Sweden, we understand that we need to pay a little more for orphan drugs than for other treatments. That can be linked to the high degree of disease severity in these patient populations. We are searching for different justifications for a separate approach to orphan drugs. This is an ongoing process aimed at gradually reducing these barriers."

Ulf Persson:
I think if we take it from the payer's point of view, we have an increased awareness that this is a big problem because it has to do with the number of patients. It is very expensive to develop a new drug or compound. To give an example, it costs about the same amount to develop a new drug as it does to build a big bridge between Sweden and Denmark, a bridge that is 10 miles long. That cost must be spread across the consumers, payers, and the patients. If we have a drug for a more common disease, the cost can be spread across many patients, with payers covering it. When we have orphan conditions and orphan drugs, we only have payments from a few patients. So, this is one of the explanations why the prices used to go up. We are talking about the prices for orphan drugs which have been considered to be a very big problem. Many times, payers are not used these higher prices. They are used to very low prices per patient, and we have traditionally talked about the number of patients treated, and so on. But now we have a situation where we can identify the patients who are most likely to respond to a treatment. That means we are treating a very small number of patients. What I have seen during the last few years, particularly from Sweden and some other European countries, is that there is growing awareness that we need to find ways to ensure a faster uptake of these drugs, rather than waiting until the patents expire or anything like that. So, there is a strong understanding that we need to develop new approaches. In some countries, like in the United Kingdom and in Sweden, we understand that we need to pay a little more for orphan drugs than for other treatments. That can be linked to the high degree of disease severity in these patient populations. We are searching for different justifications for having a separate approach to orphan drugs. I think this is an ongoing process and I can see that this is a process where we are trying to reduce the barriers more. So I am optimistic about this.

Erica Berg (host):
Annie, to what extent has the burden of maintaining sustained focus on rare diseases fallen on the individuals themselves and their families?

"Before we even had federal investments into those research pipelines and could have handoffs with industry in those spaces, it was patient groups that were doing the work of funding registries and natural history studies."

Annie Kennedy:
I like to use the saying, "It takes a crowd to draw a crowd." In the rare disease community, garnering interest in rare diseases often falls to the rare disease parents and individuals living with rare diseases. They frequently shoulder the responsibility of spurring that initial investment and interest for individual rare diseases. What we have seen is patient communities galvanize, come together, build those animal models, and drive scientific investment. Many times, we have patient communities who have been the first ones to fund the scientific communities and invest in the academic researchers who have developed the clinical trial endpoints and mechanisms and biomarkers. Before we even had federal investments into those research pipelines and could have handoffs with industry in those spaces, it was patient groups that were doing the work of funding registries and natural history studies. We have also seen patient groups de-risk participation in rare disease development, not just on a disease-by-disease basis, but collectively, by looking at where guidance is needed to better understand therapeutic development in rare diseases and where we need new regulatory pathways and new incentives for therapeutic development. We have had creative legislation and statutes, as well incentives like the Rare Pediatric Disease Priority Review Vouchers and the Orphan Drug Act. That work has, once again, been led by the patient community, to create an ecosystem that de-risks participation for investors and developers to work within our spaces, while enabling individual rare disease communities to function effectively and move products forward.

Erica Berg (host):
I think we have set the stage appropriately and I wanted to move on now to start talking about neonatal sequencing. Hadley, how has the rapid evolution and the falling cost of genome sequencing benefited the rare disease community, enabling earlier and more definitive diagnoses and potentially setting them up for interventions?

Hadley Stevens Smith:
One of the major ways that the falling cost of genome sequencing has benefited the rare disease community is through the clinical translation of this technology and through the basic science advances that have gone hand in hand with that. So, by that, I mean moving this technology from bench to bedside, so that genomic sequencing is now broadly available as a diagnostic tool in clinical care. That increasing availability in clinical care has allowed us to better understand the impacts in both the clinical realm, what we refer to as clinical utility, and on patients and their families, which we call personal or perceived utility. From a basic science perspective, those advances in understanding the relationship between genetic variants and clinical presentation have enabled scientists and doctors to make more precise diagnoses for a greater number of rare conditions. This growing evidence base, and understanding both clinical and personal utility, is very important for increasing evidence that is useful for healthcare payers, as they make coverage decisions about which tests to cover and for which patient populations. In turn, this helps make genomic sequencing gradually, and still imperfectly, more broadly available.

One setting where we know that genomic sequencing can be particularly useful in terms of establishing diagnoses and guiding care is in the neonatal intensive care unit. Genome sequencing performed early in the diagnostic pathway (i.e. the beginning of the diagnostic odyssey), for the most critically ill infants, and especially with a rapid turnaround time of less than a week, provides diagnoses for about 30% to 50% of the critically ill infants who are tested. Moreover, it impacts care decisions within a given hospital admission for about 20-30% of those tested infants. Genome sequencing can also lead to substantial cost savings to healthcare systems by informing those care decisions and by reducing inpatient length of stay. When compared with a gene panel test, which is less comprehensive, one recent analysis found that rapid genome sequencing early in the hospitalization resulted in cost savings of more than $150,000 per patient over one year from the healthcare sector perspective. Obviously, realizing these benefits, both for child population health and in terms of cost savings to the health system, requires that rapid genome sequencing be both accessible and taken up by patients and clinicians.

Erica Berg (host):
Do you have a sense of how broadly accessible neonatal genetic testing is? I know you were saying specifically in the intensive care ward, but is it accessible more generally, such as for the curious or anxious parent? What is the status of that?

"Genome sequencing is a newer technology that has been more recently introduced into clinical care, but for the past 10 years or so, exome sequencing has been available as a diagnostic test and payers are increasingly covering this test."

Hadley Stevens Smith:
There are several settings in which we can consider the use of the same or very similar technologies. Here I would lay out three different use cases. One is for diagnostic testing, such as that performed in neonatal intensive care units or in genetic outpatient clinic settings. This type of testing would typically be used to diagnose a patient with a suspected genetic condition, in other words, those whose clinical presentation warranted genetic testing. A second setting where we are seeing a rapid rise in the use of genome sequencing is in screening. As a complement to traditional newborn screening, genomic sequencing approaches are now being used to augment that neonatal screening and to expand the range of conditions that can be screened for early in life. Then, a third use case would be direct to consumer testing. We are also seeing significant growth in this market, particularly for early childhood testing aimed at understanding

disease risks and, in some cases, traits. Overall, in the diagnostic setting, both exome and genome sequencing are now much more widely available in clinical care than they were five or 10 years ago.

Genome sequencing is a newer technology that has been more recently introduced into clinical care, but for the past 10 years or so, exome sequencing has been available as a diagnostic test and payers are increasingly covering this test. That is a very critical piece of the access puzzle. This is true on both the commercial side and the public payer side. For example, there are now 18 states that have covered rapid genome sequencing under Medicaid, and legislation that would provide that coverage has been introduced in an additional nine states. This is an area with significant advocacy activity and growing recognition at the legislative level that this type of testing can provide important benefits both for families and healthcare systems.

"We continue to have a real barrier, not just with the uptake of rapid whole genome sequencing, but also with the uptake of newborn screening and other diagnostic testing across rare disease in general, is that providers, especially pediatric providers, are trained to look away from suspecting rare diseases when they are considering a diagnosis."

Annie Kennedy:
Can I build on what Hadley was talking about? Because I think it gets to your question. One of the main barriers to this testing is providers ordering these tests. Where we have seen a lot of success is within the pilots, where rapid genome sequencing has been piloted within the NICU setting and acute hospital settings. That is where we have had so many wonderful learnings and those experiences have driven so much of the momentum behind the advocacy work, such as our ability to advocate for coverage within the state Medicaid programs. Where we continue to have a real barrier, not just with the uptake of rapid whole genome sequencing, but also with the uptake of newborn screening and other diagnostic testing across rare disease in general, is that providers, especially pediatric providers, are trained to look away from suspecting rare diseases when they are considering a diagnosis. In fact, if you know anything about rare diseases, you have probably seen the zebra logo. The zebra is the logo for rare disease, not just because it is cute and catchy, but because providers are often taught that if you hear hooves, look for horses, not zebras, when thinking about rare disease and about diagnostics. Rare diseases are individually rare. That is why they are called rare diseases, but collectively they are not. I mentioned earlier that there are more than 10,000 rare diseases. That number increases every day. It is estimated that more than 10% of the U.S. population is living with a rare disease. Many people have multiple rare diseases. So, we need to change that paradigm so that providers are not looking away from a rare disease, but are adding it to their diagnostic toolbox. There are incredible efforts underway, funded by both public and private entities, that are looking at how we can introduce triggers into our data sets and learnings, so that when providers see multiple visits to an ER that are out of the norm, they can short-circuit that diagnostic odyssey. This is incredibly important. We need to do better because, as Hadley said, we have the tools and the technology, but we need to be using them. Because it does not only get somebody to appropriate care and treatment, but it also often unlocks someone's eligibility for benefits, health coverage, appropriate accommodations in schools and in workplaces, and very importantly, it enables the individual to have a community. We talk about N of 1 or N of few, but if we are identifying and diagnosing diseases effectively, we may discover that there are actually N of 2 or N of 3. We may find communities simply because we are diagnosing conditions more often. So, this is really a big plug for provider education and for shifting the paradigm around rare disease.

Mark Trusheim:
I am a health economist, like Ulf. Part of this is the cost of whole genome sequencing falling. If we did it for everyone, it would fall by another order of magnitude, which then makes the whole cost benefit analysis better for every patient. I know from a drug developer standpoint, that finding patients is very hard because they are so rare. So, having that kind of national screening and understanding is important. It also helps us from an equity standpoint, so that access to rare disease care is not limited to "billionaire babies", which is a challenge. If you are wealthy enough, you can pay for the extra genetic testing out of pocket, if it is not covered. However, if you are not, then you are often overlooked and sent on these 6- or 15-year diagnostic odysseys, if your condition allows you to live that long through the whole process. So, I think this shift, from a diagnosis-driven approach where a clinician must have a hypothesis ("I think it might be a zebra, therefore maybe I will order the test") to an approach where this is more standard like running a complete blood count, is important. They do not have a hypothesis that I have some blood issue. It is just a standard test that is run nearly every time you check into an ER. Having this done once for patients, to know what their genetic abnormalities are, seems like a fantastic tool to understand what is ahead. It may not show up in the first three months, but it will show up in the first year or it may not be until you are six or eight that you will start seeing symptoms. To be able to get out ahead of this is increasingly cost-effective and inexpensive and yet we do not provide the access to it. It could transform the whole ecosystem. It is basic and straightforward, and it would be fantastic to have this required as a standard part of care. Parents may opt out, of course, but it would be great if it could become part of the standard care package.

Erica Berg (host):
Ulf, what is the status of access to neonatal testing in Sweden and in Europe, and how are the economics playing out, particularly the balance between the cost of testing larger populations and the potential for long-term savings associated with earlier diagnosis?

"This means that we have a lot of opportunities, but also a lot of uncertainty. As a result, those who are responsible for paying for these treatments and deciding whether to introduce them into healthcare systems must make the best possible judgment they can about the value of a treatment over very long period of time."

Ulf Persson:
Yes, this also has to do with identifying patients in the same way here. One very important point is that we now can use these new gene and cell therapies that can almost cure patients or at least have the potential to do so. The problem with them is that they often involve a short treatment period followed by a long period of benefit. In some cases, it may be a one-time or single treatment that will last for many years and can more or less cure the patient. We do not know whether the effects of these treatments will wane over time or how long they will last until they start to be less effective. This means that we have a lot of opportunities, but also a lot of uncertainty. As a result, those who are responsible for paying for these treatments and deciding whether to introduce them into healthcare systems must make the best possible judgment they can about the value of a treatment over very long period. This also means that the payment should be linked to the treatment differently. We traditionally pay for the treatment, not for the benefit later. These treatments justify a very high payment because they are so effective in many cases. But we do not really know the long-term outcomes. So, we have a lot of uncertainty. This can put a lot of pressure on the healthcare budgets because they can go up to $2 million per treatment per patient, and that can be very difficult. So, we are really searching for different ways of justifying a high price and ensuring access to these therapies and getting them into the budgetary system as smoothly as possible. This is another big challenge for the payer.

Erica Berg (host):
Let us now talk about investing in rare disease treatments. Mark, can you share with us what some of the distinct challenges are when thinking about return on investment for both diagnostic and drug development programs in the domain of rare diseases where again, the patient populations are small, but the potential of these treatments to cure these diseases is tremendous.

"Some of the gene therapies cost up to a couple of million dollars, but many of them are expensive cancer therapies, costing several hundred thousand dollars a year, which is in line with what cancer treatments cost. We do not bat an eye at spending that amount on cancer, but for a rare disease, suddenly it is a problem."

Mark Trusheim:
Return on investment has two components: how much you invest as part of the game and how much you make or the revenue that comes in. Rare diseases suffer on both sides of this. The investment required to create an effective therapy for a rare disease may not be substantially lower than the investment required for a large population, such as obesity, where GLP-1s are the current hot topic. Finding ways to make the cost of developing a therapy for a small population cheaper and faster is important. We are seeing breakthroughs across the board: from regulatory improvements that speed up the process, such as requiring fewer trials or accepting endpoints that are easier to measure, to AI and gene editing techniques to help improve our success rates in finding what the right therapy is before it enters clinical trials. We have great hope there. The other challenge, which Ulf has pointed out, is once you have been approved, how much can we afford to pay for these therapies? Compared to other drugs, they can be unbelievably expensive, which seems unfair. Some of the gene therapies cost up to a couple of million dollars, but many of them are expensive cancer therapies, costing several hundred thousand dollars a year, which is in line with what cancer treatments cost. We do not bat an eye at spending that amount on cancer, but for a rare disease, suddenly, it is a problem. There are also other areas, where we do the same sort of thing, but it is not medication cost, so we do not bat an eye at funding either. We talked about neonate units. It is not unusual to incur multimillion-dollar neonatal costs, but that comes out of a medical budget, not out of a drug budget, for these payers. So, we are used to paying multiple millions to get an infant off to a good start, but paying multiple millions to give them a therapy to get them off to a good start is somehow offensive and difficult. We have children and adults with traumatic injuries. Again, the cost of treating a traumatic injury is around 3, 4, or 5 million dollars. The total cost of that type of care is not an unusual charge if you talk to the insurance companies. However, spending that amount to help a sickle cell patient not have to go to the hospital ever again is seemingly out of bounds. So, the challenge on the revenue side is that we do not compare the cost of these drugs to other life transformative therapies and treatments that just happen to fall on the medical side instead of the drug cost side. That leads to false comparisons. Another aspect that we sometimes overlook is that these therapies tend to be reasonably effective on every individual. In contrast, other therapies that we pay more money for overall, such as Type 2 diabetes therapies or statins for heart disease, you have to treat 40, 50, or 100 patients to avoid one death in those spaces. When you take the total cost of the drug, it may be lower per patient, but the overall expenditure per life saved or improved may still add up to multiple hundreds of thousands of dollars. Rare disease therapies are in a sense cursed by being effective. They help a few patients and do tremendous things, and yet because they did not have to treat 400 patients to get one to do well, like you have to do with some of these other therapies, they are somehow viewed as too expensive.

We must rethink return on investment when we consider how these treatments are paid for, and we must be able to develop these drugs faster, quicker and at a lower cost. Because if the investment were only a few million dollars instead of hundreds of millions of dollars, you would not need to make a billion dollars back just to cover the multiple hundreds of millions you spent on its development. For example, if it only costs $10 million and you make $50 million back, that is a huge return and something financial people would be very excited about. So, those are the two angles to consider

Ulf Persson:
I agree with Mark. I think that sometimes we have to budget in the benefits side as well. For example, if we give a treatment to a patient with hemophilia, as there are many gene therapies being developed for hemophilia, there is a significant drug cost saved from factor VIII treatment over a patient's lifetime. Factor VIII prophylaxis is a very big burden for the payers and if we can reduce that cost with a one-time treatment that eliminates the need for these factor VIII treatments in the future, we can free up a big budget to pay for the immediate gene therapy costs. The problem is that many times we do not have this money available. So, we need to find some clever ways to secure the budget immediately upfront, even if we understand that there will be huge cost offsets

later on in the patient's lifetime. Sometimes there is a budget available, but it is not linked to the healthcare provider in the same way. For example, we have a lot of situations for severe conditions in children where the progression of the disease means that they will require municipally funded services or home services. That is a completely different budget. But that is a budget that can be reduced if we can treat them successfully at a young age. We need to have a link between different kinds of budgets as the disconnection is another problem that we have seen so many times.

"What we have seen is that there is so much wasteful spending. When we talk about a six year diagnostic odyssey for something that could be diagnosed in the first 24 hours of life, we are talking about wasteful spending of close to a million dollars, or potentially more if we are talking about an extended ICU stay."

Annie Kennedy:
First of all, this is a sweet spot for us. As a patient community, we have done a lot of work to move from those back of the envelope calculations around what it means to live with a rare disease, to actually collecting data around the lived experience of rare diseases. We have collected data to show that in one year, the economic impact of rare disease was close to a trillion dollars. That was in 2019, and the lion's share of those costs (close to 60%) were not costs that were being absorbed by the healthcare system. They were costs that were being absorbed directly by families and the community. This really underscores both Ulf's and Mark's points that there are costs showing up elsewhere that are still prescribed but are being paid for out of pocket by families or by other elements of the healthcare system. This means that we are not comparing apples to apples when we are having these conversations.

"Investments in rare disease are strategic investments in our healthcare system, but we do not think about it that way. We must struggle and fight for funds in the rare disease space and incentivize people to work in our spaces."

The other thing is when we have these conversations around investing in therapies and diagnostics, the goal is not to cut the cost per person, it is to make strategic investments to optimize outcomes within the key therapeutic window and to eliminate waste. What we have seen is that there is so much wasteful spending. When we talk about a six-year diagnostic odyssey for something that could be diagnosed in the first 24 hours of life, we are talking about wasteful spending of close to a million dollars, or potentially more if we are talking about an extended ICU stay. I think those are the conversations we need to be having and then doing something about them. Those are policy shifts for us. The other thing is, this really comes down to a paradigm shift, and underscores something that Ulf was just saying. We need a paradigm shift around what we are willing to invest in rare disease. Mark just made some wonderful analogies about what we spend and what we are willing to risk and tolerate in other disease areas. However, we are not willing to make that same investment in rare disease research. I pulled some numbers, and when we look at what we have been spending federally in rare disease, in the U.S., we are talking about amounts that can be counted in the millions. In contrast, federal cancer funding was around $8 billion at the NIH alone, with an estimated $57 billion investment in R&D. Now, we should absolutely be investing that. About one in five Americans is estimated to live with cancer, but there is also about one in 10 with a rare disease. Should we have such a wide disparity between what we are investing in rare diseases and what we are investing in cancer? Probably not. And we are not having the same discussions when talking about what we are going to invest in a patient with a cancer therapy compared to a patient with a rare disease. We really need to be thinking about this differently.

The other thing is that when we invest in rare disease therapies, what we learn from those investments can be immediately extrapolated to more common diseases. To give an example, bisphosphonates were first studied in rare bone diseases, and they are now being used for osteoporosis more broadly in the community. When we are learning about how to treat cystic fibrosis, we are now applying those learnings to other genetic diseases. The same is true for sickle cell disease. Advances there are being applied to other rare diseases. These investments in rare disease have a much broader impact. PCSK9 inhibitors (Proprotein Convertase Subtilisin/Kexin type 9), for example, were studied in a rare genetic form of hypercholesterolemia. This is now how we treat cholesterol broadly across the world. So, these investments in rare disease are strategic investments in our healthcare system, but we do not think about it that way. We must struggle and fight for funds in the rare disease space and incentivize people to work in our spaces. We are not actually thinking about it as a public health investment.

Mark Trusheim:
We have made so much progress in science because the science was ready 20 years ago. As we began to understand the targets and went to a very mechanistic and personalized approach, progress was made. That is now possible for rare diseases. Through whole genome sequencing and other tools and techniques, we can now understand the mechanisms of rare disease in a much more tractable and rapid way than we could 20 years ago. Rare diseases are now ready for the same kind of explosion in progress that we saw in cancer 20 years ago.

Erica Berg (host):
What I am hearing is that there seems to be a stigma around investing in rare disease research, potentially just because of the name "rare diseases" and I am curious to the origin of that. Mark, you mentioned a few times that people will sometimes respond with, "Well, it is a rare disease, why worry about that?" Is it just because they are rare or is there something deeper driving this perception that rare diseases are somehow less important?

"We are now seeing more regulatory pathways that are tailored to rare diseases, but we still need more predictability and certainty around those regulatory pathways. We also need more predictability and certainty around the access environment and what the reimbursement pathway will look like for those approvals. That is how we are going to continue to incentivize development in rare disease."

Annie Kennedy:
I would say it is less about stigma, and more about the uncertainty around what the regulatory and access environment might look like. We are now seeing more regulatory pathways that are tailored to rare diseases, but we still need more predictability and certainty around those regulatory pathways. We also need more predictability and certainty around the access environment and what the reimbursement pathway will look like for those approvals. That is how we are going to continue to incentivize development in rare disease. So, from my perspective, this is not about stigma, it is about being able to strengthen those development pathways and, again, de-risk the investment. The other piece, as I said at the outset, is that we also need the resources to be able to identify who has a rare disease, to diagnose those who have a rare disease, and to build those resources and that infrastructure to support this work. That is an important part of de-risking the rare disease environment.

Erica Berg (host):
Hadley, I was hoping you could weigh in on the ethics. What kind of weight can moral or ethical arguments carry in terms of persuading pharmaceutical companies, research organizations, or grant funding agencies to commit resources to rare disease programs?

Hadley Stevens Smith:
That is a great question, and I think it also relates to the conversation that we were just having. One of the areas in which we see a lot of new and exciting investment is in genomic newborn screening. There is a new initiative from the NIH called the BEACONS program. The state of Florida has also devoted funds to start up a Sunshine Genetics program, where every baby in the state of Florida, and across several other states, as part of the BEACONS program, would have access to genomic newborn screening. Mark was highlighting the potential equity implications of expanding access to newborn screening in this way. I think one of the things that we need to be careful about is balancing uptake with ensuring the program is designed in a trustworthy way, particularly when it comes to considerations around commercialization of the data and access to the sequencing data by companies that could potentially use it to develop therapeutics for rare disease. We must balance what the community expects from a trustworthy program with how we think about broader population benefits that could come from scientific and therapeutic advances. In the newborn screening space more broadly, I do think that we are seeing investment, along with the impact of the equity argument that access to a rare disease diagnosis early in life should be equally available to all babies across the country. That access does not only result in savings to the healthcare system and help eliminate the diagnostic odyssey, but it can also serve the pharmaceutical industry and the patients who would benefit from advances in rare disease therapeutics.

Erica Berg (host):
Would anyone else like to weigh in on where these ethical obligations should play a role in this discussion?

Ulf Persson:
I would like to add that sometimes we do have a budget there to pay for the investment. The bigger challenge is when we do not have any budgets available and we just have to pay for the improvement directly. When we are talking about the health improvement, we are used to paying for extra life years, life extensions and for improved quality of life. When we are dealing with orphan drugs and orphan diseases there might be a lot of other additional value drivers. For example, the degree of severity of the conditions, which are often very severe. Sometimes the goal is to reduce the risk of disease progression, and there is what we used to call the "value of hope", paying for a chance that the patient might be one of those who respond to it, even if they are not the average people who respond to a certain treatment. This brings up new discussions about the value of risk reduction.

So, it is about considering risk reduction and sometimes accepting additional risk in cases where we have a severe condition. We must learn how to better evaluate these kinds of conditions. I am somewhat hopeful because there is a lot of ongoing research, much of it from the United States, which we are using in Europe. Many times, some of these researchers in the US are a little ahead in understanding how to acquire new evidence about patient preferences for different value drivers and get that evidence into the decision-making process for the payers and the Health Technology Assessment (HTA) organizations. They must take on these very difficult decision-making processes and get this new evidence of value into them. I think that is very important. This means we need to develop our value-based reimbursement system so that they can work for orphan drugs. There is still a lot of work to do in this area.

Mark Trusheim:
A positive trend is the increased emphasis on wellness and health, with early diagnosis and understanding people's risk as an essential part of acting as early as possible. It used to be that until you presented with something debilitating, the healthcare system did not pay too much attention. And from a research standpoint, there was not much attention given either. I think this shift is incredibly important. You are seeing it in cancer with early screening, and you are seeing it with newborn screening. That is a positive trend. I think it helps counterbalance the challenge that, as Annie mentioned, many rare disease costs are ignored because they are borne by families rather than the healthcare system. Unfortunately, for the most severe cases, death has historically been "cheap". Dying quickly from a rare disease does not cost much to the healthcare system. It therefore does not get built into how much we think we ought to spend for healthcare. I think we would be naive not to say that there is also a tension between people who do not want to see their health costs and their premiums go up as we expand. Luckily, we are getting better at treating other conditions more cost-effectively. On the drug side, I think the numbers are something like $200 billion or more in drugs that are coming off patent over the next five to ten years. That is a lot of drug spending that could be freed up for these kinds of new therapies. So, it is a great time to start swapping resources from other areas to rare disease,

as those other conditions are now going to be cheaper to treat.

Erica Berg (host):
I would now like to shift to a more forward-looking discussion. How can we foster a more collaborative environment between rare disease communities, encouraging collective progress rather than competition for scarce resources?

Annie Kennedy:
I think that in the rare disease space we already have an incredibly collaborative environment, compared to other spaces. I think this is because it does take everybody rolling up their sleeves and working together towards a shared mission, as well as an unparalleled amount of passion to dedicate towards discovery for a specific rare disease. Oftentimes, communities are convened by a patient community or a group of patient communities, so the spirit of collaboration runs deep and strong in the rare disease space. I do not think that the competition in rare is negative. I think it is probably why it fuels rare and it does not detract from the mission and the goal. I do think that we need more enhanced incentives and that we need to protect the incentives that we currently have in the rare disease space. This will help ensure that the investors and the developers already engaged in rare remain, while attracting those who are maybe standing on the sidelines into our space. Additionally, we need incentives to draw the best and the brightest in the scientific, payer, and diagnostic fields into our rare disease space, because that is what we need now more than ever.

Erica Berg (host):
I guess I was thinking more along the lines of collaboration beyond the rare disease communities, so more about getting at this tension between common conditions and rare conditions and this battle for resources. Hadley, could you share some thoughts?

> ***"In the rare disease space, we know that we often have highly motivated patient communities who are also very generous with their time. It is a true honor to be able to carry out research with rare disease communities because they are so motivated to work together and to share their stories and to move the field forward. There is always an altruistic motivation that is apparent in working with these communities."***

Hadley Stevens Smith:
Annie makes a great point about collaboration within rare. I also think that we can go back to this idea of the scientific spillover effect. So, what can the broader medical community or the broader basic science community learn from what is happening within rare disease? On the academic side of things, we often think about what we can learn from rare disease patient populations, particularly in terms of improving methods for understanding patient-centered outcomes. Those learnings can then be translated into these broader disease spaces as well. I think that it really comes down to decreasing and breaking down silos and being more collaborative, especially around the efficiency of learning across different spaces. In the rare disease space, we know that we often have highly motivated patient communities who are also very generous with their time. It is a true honor to be able to carry out research with rare disease communities because they are so motivated to work together and to share their stories and to move the field forward. There is always an altruistic motivation that is apparent in working with these communities. So, I think taking what we have learned about how patient engagement science works in rare disease and translating that into the broader medical sphere is an important take away from this experience.

Ulf Persson:
I can see concern about a new conflict that has emerged recently in my country and in some other European countries. It is a conflict between budgets for treating common diseases like diabetes, obesity, and Alzheimer's disease with the new drugs coming onto the market, and the budgets for orphan diseases. Sometimes the argument is that if we pay more for treating the orphan diseases, we will have to reduce spending on diabetes, obesity, and Alzheimer's disease, or whatever else is coming next. I understand the discussion, but at the same time, when we are talking about common diseases, we are talking big budgets. When we are talking about the orphan diseases, we are often talking about very few patients, even in if the price per patient may be high. But we are not talking about the same kinds of budgets. I think there must be some other criteria to justify the pricing for orphan disease treatments instead of evaluating them on risk reduction in the same way we do for common diseases, even though those are very important for the prevention of future diseases related to overweight and similar conditions. I understand the logic, but this is a direction of discussion that I am not very comfortable with, even if I can see where it is coming from.

> ***"If we could track symptoms with the same rigor that we track billing codes, we would have a data infrastructure that everyone, from scientists to payers, could leverage in phenomenal ways. That represents a huge opportunity but requires collaboration across many of these stakeholders."***

Mark Trusheim:
There is a clear need for data infrastructure, from natural history studies onwards. We know that Medicare and increasing numbers of other payers want to pay based on outcomes and that requires a quantitative understanding of patient experience, patient status, and where patients are at any point in time. We have a huge billing system where we track all the inputs with excruciating detail, but we collect very little data about how the patient is feeling, what their symptoms are, and what their actual functioning is in daily life. We do not collect that information systematically in the healthcare system. That would seem to be the basis for understanding real value across large population diseases and rare diseases. It would allow us to understand the natural history of all the subtypes of obesity, diabetes and cardiovascular disease as well as the thousands of rare diseases. That kind of understanding is simply not the way we practice care and or manage health today. The FDA and NIH should be commended for the many rare disease registries they have funded over the past five years. They

are in the dozens if not the low hundreds at this point. However, they are all one-off efforts. They are not part of a systematic approach to tracking the data on how well patients are doing once they encounter the healthcare system. We still lack a way to understand their symptoms and track them just as rigorously as we track how many billing codes we can put in the medical records. If we could track symptoms with the same rigor that we track billing codes, we would have a data infrastructure that everyone, from scientists to payers, could leverage in phenomenal ways. That represents a huge opportunity but requires collaboration across many of these stakeholders. It is a fantastic opportunity for us, particularly with the use of AI, as long as we follow clear rules about the appropriate and ethical use of all this information.

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