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>> Good morning, afternoon, or evening, depending on which part of the world you are Zooming in from today. I'm Mildred Cho, and I'm delighted to welcome you to our May ELSI Friday Forum, value and values in payment for gene therapies.

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This forum is hosted by the Center for ELSI Resources and Analysis, and held on the second Friday of every month for an hour, starting at noon Eastern time. We also have a Zoom room reserved for more informal discussion immediately after the panel, for 30 minutes. So we hope you'll join us there too.

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For those of you who might be new to the Center, we provide resources to support research on the ethical, legal, and social implications of genetics and genomics, and serve to connect scholars, scientists, policymakers, journalists, members of the public, and others to engage in ELSI issues.

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It's funded by the National Human Genome Research Institute at NIH, and is managed by teams at Stanford and Columbia Universities, in partnership with the Hastings Center and Harvard University.

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Please visit CERA's online platform ELSIhub.org, to get the recording and the transcript of this forum and related references afterwards.

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Please use the link in the chat to learn more about some of our featured items, and today we're gonna feature our newest ELSIhub collection, about economic patient and family evaluations of gene therapy, and it's called: Paying for Cures. Ethics and Economics of gene therapies for rare diseases. Created by Dr. Meghan Halley. We're also pleased to share a new interview,

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called engaging underrepresented communities in research, which spotlights ELSI researchers' perspectives on building trust, handling potentially stigmatizing findings, and recognizing unique ethical considerations.

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Please also go to our website, if you would like to join our ELSI Scholar Directory, to sign up for newsletters or other events like this one, at ELSIhub.org, and also to get daily updates and news on LinkedIn and Twitter.

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Some quick housekeeping about closed captioning, for example: Please turn on the CC button at the bottom of your screen.

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And in order to conserve a significant portion of our time in discussion, our panelists' presentations will be very brief, but please use your Q and A button, which you'll also find at the bottom of your screen, to write in questions at any point during the session.

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You can register your enthusiasm for questions and elevate them up a list by using the upvote button in the Q and A box. The chat box is available for further engagement, and we'll post links to resources referenced in today's discussion there as well.

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If you have any questions, please email info@ELSIhub.org, at any time.

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So I am extremely pleased to introduce Dr. Hadley Smith as our moderator. She's an assistant professor in the Department of Population medicine at Harvard medical school and Harvard Pilgrim Health Care Institute. She's a health economist and ELSI scholar.

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Her research focuses on the evaluation of clinical, patient centered, and economic outcomes of genomic medicine, primarily for newborn and pediatric populations.

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Her research on family level utility of pediatric genomic sequencing is supported by a K99/R00 from NHGRI. So I'll turn it over to you, Hadley.

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>> Thank you, Mildred. I'm delighted to be moderating this webinar on economic and ethical considerations, which we are calling value and values, of payment for gene therapies.

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Advances in gene therapies for monogenic disorders have brought hope of curative treatment. Since the Food and Drug Administration first approved a gene therapy in 2017, the pipeline has steadily increased, such that 20 new gene therapies are expected to be approved each year, starting soon.

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As we speak, today, a group of FDA convened experts is reviewing clinical data on experimental gene therapy for Duchenne muscular dystrophy, and just last month, the Institute for Clinical And Economic Review, known as ICER, released a draft evidence report on gene therapies for sickle cell disease.

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Health system decision makers around the world are facing complex issues related to value, affordability, and equity, posed by the high upfront cost of these new therapies. Traditional health economic approaches to assess value are intricately linked to values, the normative aspects of resource allocation decisions.

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Building upon discussions in the CERA-funded Value Ethics Working Group, which Meghan Halley and I co-lead, this presentation will provide an overview of pragmatic and ethical aspects of health technology assessment, which we will refer to as HTA, and payment models for gene therapies, from an international perspective.

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The World Health Organization defines HTA as: A systematic and multidisciplinary evaluation of the properties of health technologies and interventions covering both their direct and indirect consequences.

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It is the multidisciplinary process that aims to determine the value of the health technology and to inform guidance on how these technologies can be used in health systems around the world.

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Speakers will discuss the value-relevant characteristics of gene therapies that distinguish them from small molecule drugs, the ways in which gene therapies challenge traditional approaches to HTA, and how HTA has shaped decision making across jurisdictions,

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as well as novel payment models for high cost, high value products. The ethical and legal landscape will be explored, as well as ways in which empirical evidence on value relates to questions of equity and access.

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Now I will briefly introduce our two speakers. First is Dr. Renske ten Ham, an assistant professor at the UMC Utrecht in the Netherlands, and specializes in health economics and health technology assessment of regenerative medicines.

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Trained as a pharmacist and with a masters of science in HTA, she holds a PhD in drug innovation, titled: Development, market authorization, and market access of gene and cell-based therapies.

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Over the years, Renske conducted research at the University of California, San Francisco, spent time at the Dutch Medicines Evaluation Board, and the National Health care Institute in the Netherlands. Renske strives to facilitate translation of regenerative medicines by identifying and mitigating regulatory and HTA challenges to increase patient access.

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She believes insights from past challenges will not only benefit these products and therapies now, but also future biomedical innovations.

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Our second speaker will be Dr. R Brett McQueen. Dr. McQueen is currently a tenure track assistant professor at the University of Colorado, Skaggs School of pharmacy and pharmaceutical sciences and a member of the center for pharmaceutical outcomes research, CePOR. His research interests include comparative effectiveness research, cost effectiveness applications, and methods development,

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value-based outcomes contracting, and patient preferences research. He's active in the health economics related societies, such as the International Society for pharmacoeconomics and outcomes research, ISPOR, through contributions to ISPOR short courses, workshops, issue panels, and research presentations.

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Dr. McQueen has led or collaborated on modeling submissions for health technology assessment since 2016. He has authored over 60 publications in journals such as pharmacoeconomics, diabetes care, and medical care.

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He is the course director for a PhD course, applied cost effectiveness modeling. And with that, I will turn the floor over to my colleague, Dr. Renske ten Ham.

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>> First of all, thank you very much, Hadley, for the invitation. I will quickly share my screen and see if I can do two things at once.

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There we are. Thank you very much for the opportunity and the invitation to talk to you today about value and values in payment for gene therapies.

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My compliments for the title. It's really catchy. And I think very broad. Thank you so much for the introduction.

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Before I head off into a variety of topics, I would first like to start off a bit about the context in which I'm approaching this. And that might be quite a bit different from your context.

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So let's get aligned first, a bit. And then after that, I'm very interested in what you think, what your take is on this. So when I think about gene therapies, they're part of an innovative medicinal product group called advanced therapies in Europe, or advanced therapy medicinal products.

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And how I see them -- and Hadley already touched upon this briefly -- is that they are really amongst some of the most innovative medicinal products we have currently. And when we compare them to small molecules, there is really an innovation step, based on those technologies, and manufacturing, for example, quality assurance, as well as science,

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as well as a biomedical advancement, that allowed us to bring biologicals or larger protein-based drugs to the market in a safe, effective way. And I believe that advanced therapies are another innovative step from those biologicals.

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And going from left to right, innovation has occurred over time. But also, complexity increased over time. From small or smaller molecules to larger molecules. Biologicals. And to even larger molecules, to live cells, live tissues, as well as gene therapies, where we are able to alter part of our DNA and our RNA.

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But also, uncertainty increases from left to right. Uncertainty around evidence, uncertainty around safety and efficacy, uncertainty around how to properly manufacture and quality assure these types of products.

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But what I find really interesting is that if we go back somewhere, about 20 or 30 years in time, and dig a bit deeper into sources such as, for example, PubMed, we see very similar articles, as we see today. For example...

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Biologicals are they too expensive? Are they only there for orphan products? Are they only... How can we regulate them in a safe and qualitative way? And assess them? And we see sort of similar articles now pop up. Which gives me the hope that over time, we learn.

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Biologicals are part of our very regularly used drug repertoire. And they're pretty much seen as business as usual. So I think there will be a time that these advanced therapies will... And gene therapies are of course part of them. Be business as usual. But we're not there yet. And it will take us a lot of time and effort.

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And radical new products don't fit into new frameworks overnight. So to start off with a positive note -- also I want to encourage us to keep organizing sessions like this, and encourage discussions to see how we can get these gene therapies into... To fit into our drug development and assessment frameworks.

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And then perhaps there will be other innovations, in which we have advanced drug therapies in which we can focus our efforts on them.

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So we're going to talk about value and values. And I'll touch mostly upon the first, value. So the economic, monetary values. Because as a health economist, that's what I work with the most. And this is a very stylized example of how cost and how that value of gene therapies differ so much from what we're more commonly used to.

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So, for example, chronic therapies, or small molecules, or biologicals. And how exactly do they differ? This is an example of cost over time. So effect is not taken into account here. Of a gene therapy. In this case, the yellow line resembles the cost over time for a hemophilia gene therapy. And in green and in blue, you see the prophylactic treatment, the chronic treatment.

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Before gene therapy came to market, that really was the standard of care. And what we see here -- we look at the cost of chronic therapies over time. Cost accumulates over time. Right? Because you need frequent administrations of these drugs.

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But it also makes them very predictable. So you know on average what a hemophiliac patient costs, drug-wise. But if you look at that yellow line, that gene therapy, then all at once, at the start of that treatment, that high up front cost... Has to be... Is all at the front of the time of admission. So T=0.

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Over time, less cost accumulates. But it's actually really that discrepancy between predictable accumulating cost, over time, of these prophylactic and chronic treatments, that we're used to, and the difference really leans on that high upfront cost for these gene therapies, that really makes paying for them quite difficult.

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Because it has a high budget impact. And you can imagine that it's really nice to have a prolonged benefit over time. But if you have a new therapy coming to market, on a small budget for drugs, as a payer, then you have the chance that this new one-gene therapy can blow up your whole pharmaceutical budget all at once in the beginning of the year.

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And you have nothing left to pay for other chronic treatments. To give a very stylized and black and white example. In my opinion, that really is the difficulty, where this lays, paying for these types of therapies. And there are different ways to address this. Brett will talk about them a bit more. Very interesting, and also very timely.

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But in addition to that high up front cost, there's also quite some uncertainty about the time of the sustained benefit into the future. At time of assessment. So, for example, if you have a gene therapy that has a promise of having a long effect, but in reality, it only has a proven effect of about two years, then you would say...

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Well, actually, if you're going to pay for this gene therapy or you have to pay for the prophylactic treatments, I guess the choice is quite simple. It's a lot more expensive to pay for the gene therapy. But what if the evidence of the gene therapy is... Well, it's about 7 years in this case? Then I guess there's somewhat of a break-even point. Right?

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It depends on who you compare it with. But there's a high chance that you could actually end up saving costs. But... What if this gene therapy turns out to be effective for ten years or perhaps even longer? Then I guess it's kind of a no-brainer that we reimburse this gene therapy. And that we actually have really good value for money.

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And the difficulty herein lies that at time of assessment currently, because these are such novel therapies, it often is not very clear or perhaps only in subgroups of patients... How long these effects actually will turn out to be. And there's high uncertainty around that.

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So the combination of the uncertainty around long-term benefits, combined with those high up front costs, really make paying for these therapies... Their affordability really a key issue. And yet, this is a bit of -- previously, I only showed you the cost over time. This is a graph that actually takes into effect the benefits. So the blue bar is actually the gene therapy, compared to a prophylactic treatment called factor VIII.

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And the green is the comparison of the gene therapy in comparison to a biological, emicizumab. So high up front cost -- if you take into account the benefit, in the first couple of years, you pay too much for the benefits you're receiving, but over time, because the costs stay quite steady, you actually go from a negative net benefit, to actually a positive net benefit.

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And at some point, there will be a break-even point. That is when that yellow line actually crosses that green or that blue line in the previous graph. But when that point occurs is really uncertain. So also thinking about ways to mitigate this -- for example, via payment models.

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And it's really important to have a sense: Is that payment model going to take -- going to organize that for three years? For five years? Perhaps for ten? I'll leave it up to Brett. If it's sensible to have a payment model running for ten years. But actually that sort of return on investment point or that break even point is quite interesting to have a sense of.

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Because then you'll know how long it will take for you to have that high up front cost, and get a sort of a payback on your up front investment in health. Which from an ethical point of view is quite interesting and could raise quite some eyebrows.

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And as I mentioned before, uncertainty is quite difficult. Because how long does that product work? Right? How long is your treatment going to be effective? And I showed you this graph before. But what I'll do now is I'll add the 95% credibility interval, or the uncertainty. And what you'll see is there's actually really high uncertainty. Right?

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And this is a really interesting case, because it's for hemophilia A. And this specific product, we saw that a couple patients really had really long benefit from these therapies. But a couple patients were also within a year or two years... Had to go back to their chronic treatments. And that's really what is actually behind the high uncertainty portrayed in this picture.

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But what we currently do not know for this specific indication is how we can up front identify which patient will and will not benefit. And this is one of the keys, amongst a lot of other uncertainties, which I think we really need to address, to make sure that we... Well, try to spend our money as good as we can.

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Because we have fixed health care budgets, but we have a lot of needs, so we have to make choices. And health care technology assessment... Is something I should give a definition of... Actually really helps us to prioritize what we could or should or can reimburse. This is an example for hemophilia A. There are other gene therapies for, for example, hemophilia B, and other types of indications,

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and we are a lot better or there's less uncertainty about which patient will and will not benefit. So you see the confidence intervals are actually a lot smaller, and perhaps the decision to reimburse or not reimburse might become a bit more easy. Although never fully black and white in my opinion, so far.

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So I was also asked to tell you a bit more what my take on this is, from a European perspective. So what I'm showing you here is a table that is really a rough table, but I'll take you through it bit by bit. On the left, you see all the cell and gene therapies that have been approved in Europe.

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And on the right, you see what the reimbursement decisions were or recommendations were for Scotland, the Netherlands, and England. And what you actually see in green are products that had a positive assessment. Either with or without any restrictions. And red, negative. And what you see up front in the top is a lot of white.

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That means that developers actually did not submit their products to HTA bodies. Because a lot of these products were actually already pulled from the market due to commercial reasons. I'll get back to that in a bit. Commercial reasons mostly being that they did not receive any reimbursement or were not commercially viable.

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Throughout the time, we actually see that more products were offered to HTA bodies. You see a bit more red on top and a bit more green on the bottom. That indicates that there is a bit of learning on the developer's side, or the HTA body's side. What evidence is needed to do these assessments. But I think what also is quite striking is that we see there's quite a difference in recommendation.

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Some products are recommended in certain countries. Some are not. And there are several reasons for this. I'll highlight a few. But there are actually many more. And it is because although we have -- in Europe, there's actually a public health care funding system, it's very different, compared to the US.

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But actually, every country has their own HTA body. And here you see it's a bit of an older picture. A lot of different logos. But even countries, for example, such as Italy, as well as Spain, they have more than one HTA body. Meaning that decisions on whether to reimburse or not actually differ sometimes per region in a country. Because other bodies are responsible.

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And might take different decisions. And these health technology decisions actually are -- several considerations are important. On the bottom left, you see the ICER, the ratio that you probably have seen before. That's a quantified golden outcome, when it comes to cost effectiveness modeling or economic evaluation.

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So that's very much the blue ECO, cost or economics considerations. But what you see here are also included. Ethical, organizational, societal, for example. And what we see is that there is a lot of policy around whether to reimburse or not. It's based on different indications, high unmet medical needs, pediatric indications, or end of life indications, for example.

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Different domains are weighed heavier. For example, we're willing to pay more for indications with high unmet medical needs. Therefore the ethical or social domains weigh more. And we are willing to pay more for these indications or to provide drugs for these therapies.

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And gene therapies are often amongst these. And going back a bit to the differences between countries -- what we see here, and I'm throwing a lot of quite heavy graphs at you. I'm very much aware of that. But what you see here is: The gene therapies are required to be regulated by the European Medicines Agency.

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Which is for all of Europe at once. Which is very different from other types of drugs who can seek only national regulatory approval. Gene therapies by law have to go through the European procedure. And what you see here is that the EMA makes a benefit/risk -- solely only based on one product, weighing whether or not the benefit outweighs the risks.

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And they ask a whole bunch of different types of evidence for that. So that's the first graph. But what you see regarding health technology assessment -- that different countries actually ask for different types of evidence.

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And they also weigh that a bit differently. And that also is one of the reasons why, based on similar evidence, perhaps, from a clinical trial, right? Because a lot of gene therapies -- their evidence is based on small or single arm clinical trials -- actually, because different evidence, or different additional evidence is requested by HTA bodies, as well as weighed in a different way,

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that leads to different outcomes. Which I always find very... Difficult to explain, for example, to patients, who might... We see this often, actually, in the Netherlands -- who do sort of an outcry of help. That they have a sick child. And in the Netherlands, there is no reimbursement for a product that is so close to market and has regulatory approval, but there is reimbursement for it in Belgium. And I find that really difficult to explain.

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But this is one of the reasons why that actually is the case. And what you also see, at the time of assessment, or the time an HTA body takes to actually conduct the assessment, varies quite a bit. So the products... Hypothetical products I just referred to could now already be available in Belgium, and may still be under assessment in the Netherlands.

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So there's also a bit of a lag time between all these countries. This could be also in part due to different assessments of regulatory bodies, as well as market assessment of companies. And I talked already a bit about some sort of a learning curve. Right? Because I believe if we have radical new technology, then researchers or developers are also really learning how to maybe...

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Manufacture these types of products. And what we saw that: For example, the regulatory body in Europe, the EMA, really went also through a learning curve, in which they really had to come up with a whole bunch of new legislations or regulations on how to assess this.

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And I truly believe that actually, at the moment, HTA bodies are also somewhere in that position. So this is a really nice visual of a former colleague of mine, in which she actually asked HTA bodies: Okay. How often do you consider a specific technology in their health technology assessment as complex? Advanced therapies, including gene therapies, are really on top of this. The weighing of cost, as well as uncertainty...

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As a researcher, I find this really interesting to work with. But you can see that this visual might also indicate that HTA bodies are also struggling with this. And we see slowly but surely HTA bodies across Europe thinking about or rolling out or piloting guidelines in which they have alternative assessments, or in which they propose different types of methods on how to assess these products properly.

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And I'll move towards the end here. Because... Translation of new products takes time. Right? And we really see throughout the time -- and perhaps one of you are maybe historically also interested in gene therapies, that we saw -- some successes, and then, for example, really terrible adverse events occur, and then interest plummets. Both from patients, as well as physicians, as well as, for example, developers and investors.

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And then a breakthrough occurs, and interest peaks again. But I really think that we can look at successes from different types of... From different perspectives. And this is a really interesting example. Unicure. This is a product... The company is called Unicure. The company is

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The product was indicated for high cholesterol. This was pulled from the market really quickly and only one patient was ever treated with it. Although that might be successful from a health perspective, as a health economist, I would say this is not a very successful product, but in the course of gene therapies, this is a really successful product,

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in the sense that it was the first gene therapy ever regulated or assessed by a regulatory body, which is very new for a regulatory body, and I believe it truly paved the way for other gene therapies to come after. Because it proved that we can assess these products within our regulatory framework.

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And thereafter, it did not receive any reimbursement, so the HTA was not that big of a success, but I truly believe that we learned from this case. And if you have any time left, or are interested in this, there are some really interesting scientific papers. The historical path of this product and what went well and didn't go so well and what we can learn from it. It's really interesting.

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This is my last slide, and I'll turn it over to Brett. But... As a former health economist, it's really easy to think about -- reimbursement has been reached, and that is the final goal. And that might be the case more for small molecules and biologicals, but when we talk about gene therapies,

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market access is definitely not the same as patient access. Because especially if we think about the ex vivo gene therapies, the CAR-T products, which are very difficult so far. Who knows what innovation might bring in the future. Prediction pathway -- and there's also quite some learning. Regulatory learning, HTA learning we're in the midst of, and we're also going towards clinical learning.

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And how can we actually make these products efficiently and safely and keep them safe for the patients? Most of my audience is from the US and also European listeners -- but what about the Third World or developing countries? So that's something that we're already hopefully thinking about addressing.

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But after we have solved all of our HTA or market access type challenges, this is something we really have to start thinking about. How we can address this. And not only to make these products available, again, in Europe or in North America, but also in other countries.

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Because they can really help this long, sustained effect for more remote populations. So this is more of a future outlook. And I'll leave it at that. Thank you very much for now. And I'll hang around of course for the Q and A. And I'll hand it over to Brett to talk more about reimbursement models. Which is a really interesting topic. Thank you.

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DR MCQUEEN: Thank you, Renske. That was great. Hadley, can you just give me a thumbs up that you can see that?

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>> Looks good.

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DR MCQUEEN: I'm Brett McQueen at the University of Colorado. And just to acknowledge our team, at the bottom there, there's a lot of people working on this project.

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And we do appreciate the support from HCPF, or Colorado Medicaid. However, the comments today are my own. And they're really derived from some of the evidence generation work that we're doing separately.

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The data also, to be very clear, is not from HCPF or Colorado Medicaid. It's a subsample of IQVIA PharMetrics, which is a large vendor in the United States. So I thought it was a great discussion, that Renske had, and Hadley kicked it off really well.

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That there are unique challenges in paying for cell and gene therapies, just from a global perspective. It's really disruptive. This is a brand-new way of thinking of therapeutic interventions. But even more unique is the challenging position that US Medicaid is in. With paying for cell and gene therapies.

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Because they're required, mostly, to cover treatments for manufacturers with a best price in place with CMS, that leaves them with really no choice but to pay for these often one-time treatments, with high price tags. There's a ton of variability, by the way, in the cell and gene therapy pipeline. I think it's generally thought that these are very disruptive. Could lead to massive cost offsets for the health system.

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And while we're doing the entire pipeline review for Medicaid, we're finding that's pretty far from the case in every therapy that's approved. You could have a therapy that provides no additional health benefit, with massive cost offsets, all the way to a therapy that provides significant health gains for patients, and no cost offsets, and everywhere in between.

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So that's really where value-based contracting approaches are starting to gain some momentum. We want to decrease our uncertainty in our budget projections, and we also want to improve access for patients. And if you're not familiar with value-based contracting,

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it's often used -- there's a lot of other naming conventions. These are just umbrella terms. Where we have this agreement between a manufacturer and a payer. It enables access to a particular therapy, but also subject to some conditions. These other naming conventions, I would just say, if you see any of these...

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We're all generally considering the same concept. But they might be split by type. And I think this figure is probably the best to characterize value-based contracts or managed entry schemes. Because they usually fall into two buckets of financial -- so that could be volume or expenditure caps -- we've been doing that for years in the commercial market in the United States. That's not really a surprise.

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On the right hand side are more performance-based. So if I pay for this therapy, I want somewhat of a guarantee that it's gonna work. And if not, either I won't pay for it, or I'll get a rebate back from you, after I've paid for it up front. And then of course we're finding there's actually a merge between these. There's overlap in certain cases. In some of the contracts that we've been negotiating.

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So why would we use value-based contracts? I mean, some of the motivation was already presented. We're already executing these contracts in a Medicaid setting, where there are a lot of competitors. Right? It increases our leverage, our negotiating power.

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But with cell and gene therapies, it's a different problem. We have this launch of potentially high budget impact items. And then also really high overall drug spend in previous years. And that's really probably specific to cell and gene therapies, moving forward.

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NEWDIGS -- they were based out of MIT. They're now based out of Tufts. And they've conceptually been talking about this for a few years now. This is just one example of a milestone-based contract that is more -- not necessarily a guarantee. It's pay by result, instead of getting a rebate. Same general concept.

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We give some initial up front payment. We assess the outcomes over time. And then there's a rebate, based on performance. This is really pretty typical in what's suggested. But -- and I'll give you a case example, for severe hemophilia A. Because this is coming in basically a few months. Medicaid is gonna face this problem very soon.

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And if you've heard the term Roctavian, it may have been connected to its $2.4 million price tag. You probably think... Wow. That is a huge price, until you understand how much Medicaid is already spending on severe hemophilia A with prophylaxis or factor VIII therapy. We identified really three main uncertainties, not only for Roctavian, but for other cell and gene therapies.

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First, everything that's based out of the literature, in terms of cost of illness, are generally averages of a specific cut of the population. They really are not capturing the variability in usual care spending, versus observed data specifically from Medicaid. Not necessarily in the commercial market. Second, how effective are these therapies gonna be?

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I mean, we have maybe a few years of trial evidence from phase II, and maybe phase III, and the drug is approved, and now we have to use it, and diffuse this into the population with no knowledge of: Is that durability of benefit gonna last 7 years, 10 years, 15 years? And then finally, there's a real lack of guidance on eligibility criteria.

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How severe does your severe hemophilia have to be, to be eligible for the therapy? Not only that. Will patients choose to take a one-time infusion, therapy versus being on prophylaxis, when they've been used to that, for really their whole lives? Or at least, for some patients?

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So I won't go through in detail with the methods, but I really just want to note that our aim is to try and demonstrate the risks and uncertainties, not only for Roctavian, but for all of the cell and gene therapies that Colorado Medicaid is gonna face. And we're proposing probably... You know, in combination, they're unique.

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But fairly traditional methods of using claims or clinical practice data, combined with simulation models, to identify some of these budget-neutral scenarios, and then also, with another objective, of increasing access and making sure patients have access to these therapies -- it's a difficult task.

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But I hope I can show you that it is doable for Medicaid. I spoke a little bit about the literature-based estimates. This is an example. This is from PharMetrics. IQIVIA PharMetrics. And in the literature, a lot of what's been reported is an average between $500,000 and $1 million per year, to treat this population with factor VIII. Really what we're seeing is -- that's really the Top 10% of patients in Medicaid.

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Between Top 10 and top 25, the difference is pretty stark. In fact, it's double the spending. Even among the top 25%, we're already spending $225,000 a year. So where you put the mean to base your contract on has massive implications for the potential cost offsets. It's just... Cannot be understated that this is the uncertainty that Medicaid faces, and of course, we're preparing a paper to talk about this.

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The overview -- this is an overview of the proposed agreements. I know it's very detailed. But I wanted to give you a real specific example of what we're talking about with these agreements. So let me just take a couple of minutes and explain this. On the left hand side, you'll see we have a warranty or a guarantee. And it can either be at the per-patient or the population level.

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The concept is that we pay up front to the manufacturer. We will pay the full price, and then based on when a patient reverts back to standard of care, back to that factor VIII use, there's some sort of reimbursement, based on the original payment. That de-escalates, as you move down and get further out in time.

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On the right hand side, you have what's also known as the Netflix model. Which really became popular with HepC therapies. When they were first released. And a couple of states -- I believe it was Louisiana and Washington -- used the Netflix or subscription model. And the general concept is:

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We can't afford to pay, to clear this virus, from the entire community in one year. So what we'll do is pay you a fee every year, or every quarter, over time, in order to smooth our budget out. But if you take these in isolation, in both of these concepts, in isolation, they don't address the three uncertainties that I talked about.

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Leaving Medicaid highly exposed, either financially or from a perspective of not covering therapies for their beneficiaries. If we combine both of them, first the warranty model reduces our uncertainty around the durability of benefit. It gives Medicaid some sort of guarantee that if this doesn't work, and patients go back on factor VIII, and that then comes into my budget...

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I've got a payback on that. And then the subscription model helps us reduce uncertainty in our budget projections, while also maximizing access for patients. The answer isn't one or the other. It's both. And we're trying to demonstrate this in an upcoming paper that is hopefully pending submission in the next month.

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Just some final thoughts. And any of those details, by the way, I'm happy to speak to those, as we get to Q and A. But I just want to make sure we have enough time for discussion. And some final thoughts about this: You know, I think the variation in cost offsets and benefits to patients is dramatic.

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And I think it's a total underestimate, by everyone in our field, to say: Every cell and gene therapy is curative. Or results in massive cost offsets. That's just not the truth, based on what's in the pipeline. There are a number of very disruptive therapies that will be really beneficial for patients. But they're not always gonna lead to really high cost offsets.

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And I think it would be really helpful from this group to hear... You know, what sort of framework are we walking into, with -- how do we value these therapies? When we're faced with mandates against conventional cost effectiveness analysis? It's just detrimental to our understanding of value, and to be perfectly frank, it just does nothing for us, but distract -- to distract the debate that we're having on access to these really important therapies for patients.

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And then I'll jump back up, before I pass it back to Hadley. The bargaining position of everyone separating state by state Medicaid -- it's not helping anyone. Especially when we're treating rare diseases. We're better off combining the states and going in with one type of a model that a bunch of states can agree on. And I say that, knowing that they're already proposing that. CMS is on it. CMMI had a whole report. That link at the bottom.

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That's really helpful. They have a separate cell and gene therapy payment model. But really, that hinges on understanding the patient-level data. And combining some of these agreements. You can't really do that and go to a manufacturer, and actually leverage your argument and negotiate, unless you come in with what I would say is a mountain of information, and an army of beneficiaries, to really make that argument.

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So I'll pass it back to you, Hadley, and I look forward to the discussion.

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>> Thank you so much, to both Brett and Renske. We'll now move into the Q and A session. So... I will start off with just a question to help clarify a few terms. So we've heard: Cost effectiveness, value, and then we also had an audience question about the term affordability. For Medicaid.

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So Brett, I'll address this question to you. Can you just clarify the explicit connection between cost effectiveness, value, and affordability?

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DR MCQUEEN: Yeah. Thank you for asking that question. Because some of this is such lingo. But really, when we talk about value, something might be...

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Of great importance to the population and valuable, but it doesn't necessarily mean it's gonna be easy on the budget. Affordability really means: How affordable is it for health systems to pay for this? Whereas value might be... Something a little bit broader. More hard to define. One of the clear examples in the United States was...

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The use of PCSK9 inhibitors, when they were launched in I think 2015. And the price tag was very high. When ICER released a report suggesting the price should be somewhere around $5,000 per year, instead of $14,000 per year, one of the manufacturers did exactly that. Dropped the price, just to prove the point, that payers did not want to pay $5,000.

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Because it's such a highly prevalent condition. It's cardiovascular disease. And so a lot of that affordability and value have to work together. And by sort of... I would say by minimizing our access to value and mandating against it, we're really shorthanded in understanding the value of these therapies, and also the affordability.

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>> Thank you. I'll move now to an audience question. And Jennifer asks: Would love to hear the panelists talk about the role of patient engagement in the HTA process in both of your jurisdictions. Are the outcomes that are valued by payers/HTA bodies the same that patients value? And how can we ensure that the patient perspective is appropriately represented?

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So Renske, if you want to start first?

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DR TEN HAM: Sure. Of course. I think that's a really important question. And we didn't address that, no. I know in some jurisdictions, patients' views and experience are really formalized in frameworks. And others, not so much. To give you an example, in the Netherlands, when HTAs are conducted by the Dutch National Health Care Institute, there is a possibility for patients

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to speak and give their opinion on their experience, on their disease, as well as the treatment. And I know that that's actually very much valued. More formalized is the role of physicians, or professional groups. Which of course also share their experience on treatments. But I think that's different, actually, from patient views.

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I think in these types of therapies, patient views are a lot more important than before. Perhaps a bit of a different role. To give you an example, I talked to a hemophilia patient quite often -- and they say, actually, hemophilia is a condition that's really well treatable. But as soon as patients go on to their gene therapy, they actually only then realize what the relief of freedom of disease burden, for example...

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So they feel like they actually have a really good quality of life. Up to the fact that they then realize they don't have to give themselves these prophylactic IV factors. And all the hassle that is associated with it. And then when the gene therapy stops working, they have to go back to that prophylactic factor. They actually find that they're a lot worse off.

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Roughly spoken. So... And the way to measure this -- it's not really... We don't really have any questionnaires, or ways to measure this. And put this into the effectiveness parts of cost effectiveness. Utility or quality of life. So I think from a research perspective, that's something we really need to work on. And that really makes the qualitative part of having patients involved in this...

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Hearing them talk, having their statements -- really, really important.

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>> Great. Thank you. Brett, did you want to add perspective from the US there?

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DR MCQUEEN: Just to say: Patient engagement is a key part of value assessment. And groups like ICER, who I collaborate with, have a whole patient engagement framework. And then Medicaid invites patients to comment as well, at what they call drug utilization review meetings.

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>> Great. Thank you. So next we have a question from James. Do any of these models compare the value of investing in these expensive therapies that affect a few patients, versus investing the same amount in population health interventions, that may benefit many more people? Sort of a distributional question. Brett, maybe I'll throw that to you.

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DR MCQUEEN: I think it's a really good question. However... That's exactly the pushback that you get from policymakers in the US. That if we start comparing across disease areas, then we get this hint of what they're scared of, which is rationing health care to different groups.

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And that's really been the source of a lot of the pushback against conventional cost effectiveness. And we don't have necessarily a fixed budget, like, say, a country like Britain. Which does have a very fixed budget. And they have to allocate across different disease areas. Whereas we don't really do that. We only compare within indications and within populations.

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So it's been deemed... I'm not... It's not my terminology -- but it's been deemed unethical to do that in the United States, despite, I think, a really important question that you ask. And I agree with where you're going.

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DR TEN HAM: I think actually, if I might add to that, this really goes onto the occurrence of displacement. The 2.5 million number that Brett quoted on this sheet -- for one patient, one treatment -- that's only actually just the drug. Right? There's actually also a lot of care associated with... I'm currently working on estimating with a couple of people.

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But it's not just the drug cost. It's also the care associated with administering the gene therapy. How many vaccines can you buy for that? I think gene therapies, because they're such high budget impact... There's really a big chance of them actually... Displacing other types of care.

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And if you have fixed budgets, that's a real risk.

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>> So Brett, you had mentioned that pooling patients across states could help reduce some of the uncertainty that we see, and also help improve patient access to rare disease therapeutics. What policy challenges do you see related to establishing some sort of a central mechanism in the US for access to cell and gene therapy?

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DR MCQUEEN: I mean, it's probably a better question for CMMI. But since I'm here, I think... You know, they're gonna run into challenges like data sharing, across states.

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And whether states can agree, legally, whether their budgets are set up the same, because legislatively, they may have different budget concerns. And in Colorado, for example, we proposed payment models that simply just didn't work.

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They would actually have to go to the state Congress to get the budget changed, to make those payment models work. So a lot of it is detail, I think, rather than conceptually -- everyone sort of agrees this is the best way to do it. But not every state agrees to this, based on the politics, in those individual states. So I don't really have a better answer beyond...

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If we can merge together politically, it's very feasible to do this.

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>> Renske, I'm curious if you have anything to add to that, given the experience -- the graph that you showed across Europe. That there's rarely sort of concordance on decisions by HTA bodies.

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DR TEN HAM: Yeah, well, actually... The challenges that Brett mentioned are also very... We run into them in Europe as well. Because if there is a gene therapy -- mostly for orphan diseases, you have one patient in the Netherlands and two in Belgium and three in Germany, it would make more sense to pool them.

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In some way, if you want to do some kind of evidence -- coverage of evidence generation type scheme, to make it accessible... But often, practical stuff that really... Makes it difficult to do that -- right? So sharing data for patients across countries, registering them the same way. Who owns the data? Who is gonna pay for actually gathering that information?

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And the Belgian system is very different from the Dutch and German one. So who pays for it? And I would like to know what Brett thinks of this. The theory of payment models is really great on paper. It mitigates a lot of the risk we're talking about. But I think the devil really is in the practicality of this. How are we gonna make it work in the real world?

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DR MCQUEEN: I would agree with that. I think there are a lot of legal challenges with value-based contracts. And an example we had was... We finally executed an agreement. It had come completely between the two teams. Medicaid and this particular manufacturer.

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Had come to terms, and we said: Okay. I think this is great. It's a totally unique agreement. No one has ever signed it. And then it went back to the company, and they said they didn't want to do it, and they sat on it for a year! Requesting that CMS change their legal template.

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And then finally, CMS, after saying no so many times... They all finally signed the agreement. And you know, there's a cost to that. That patients don't have access to that therapy, because we're in a disagreement over the language. So there's... What we would call an opportunity cost to that kind of argument. So that was unfortunate.

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But luckily, it finally got signed.

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>> Okay. We have time for one more question. This question comes from Tim. Is it challenging to measure patient reported outcomes because of the subjective nature?

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Or the inconsequential measurable change, even if there was a measurement tool available? Such as an increase in some economic factor associated with employment, or possible results of increased mobility to work?

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So Brett, maybe I'll throw this to you. If you can speak to some of the challenges that you've faced in maybe picking outcomes that are part of those outcomes-based contracting agreements. And to what extent the patient voice is represented in those outcomes.

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DR MCQUEEN: Yeah. It's a good question. And a lot of what we're... There's a lot to it, actually. I'll try to be focused. But... You know, first of all, largely, we have claims data. Which does not include patient reported outcomes.

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So even if we were to design an agreement, we don't even have access to patient reported outcomes. Second, if we do, and there's some supplement that's agreed... It's not really clear whether the patient reported outcome has a clear link with the endpoint that is more budget-focused.

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So then you have this sort of discrepancy in those two outcomes. And then finally, you actually have ways to link cost and quality of life. Yet, we are banned from doing so in the United States.

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So even if we wanted to do it, it's really not possible to do it here. Because of what I think is just totally distracting legislation that has nothing to do with the actual problem.

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>> I'm sure there are many people in the audience who would like to continue that thread of conversation further.

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So thank you so much, Renske and Brett, for incredible presentations and for engaging with these questions. I'll turn it over to Mildred now, to wrap us up.

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>> Thank you, everybody. I'm sure I speak for all of our attendees in saying that we learned so much from this wonderful panel. And so for those of us who can, please join us in our post-forum discussion.

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Which is more informal, and we can get to some of the questions that we didn't get to. You can just do that by clicking on the link. In the chat. That... It's there now? Yes. It's the one about continuing the conversation.

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And we hope to see you on June 9th, for our next ELSI Friday Forum. It's called legal and policy challenges to privacy in the postgenomic and post-Dobbs era. Which is gonna have panelists Natalie Ram and Alta Charo, moderated by Frances. So please visit ELSIhub.org and subscribe to the newsletter if you want more details.

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You'll also receive a postevent survey, so I encourage you to complete this, as our organizing committee really depends on your comments and takes your suggestions seriously.

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It's informing us on how to improve this forum, and bring new topics and speakers to you. So please do fill that out. And I wish you a wonderful weekend. And hope that you can join us right now, for the continuation of this conversation.

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In the link, if you click on the link that's in the chat. Thank you very much.