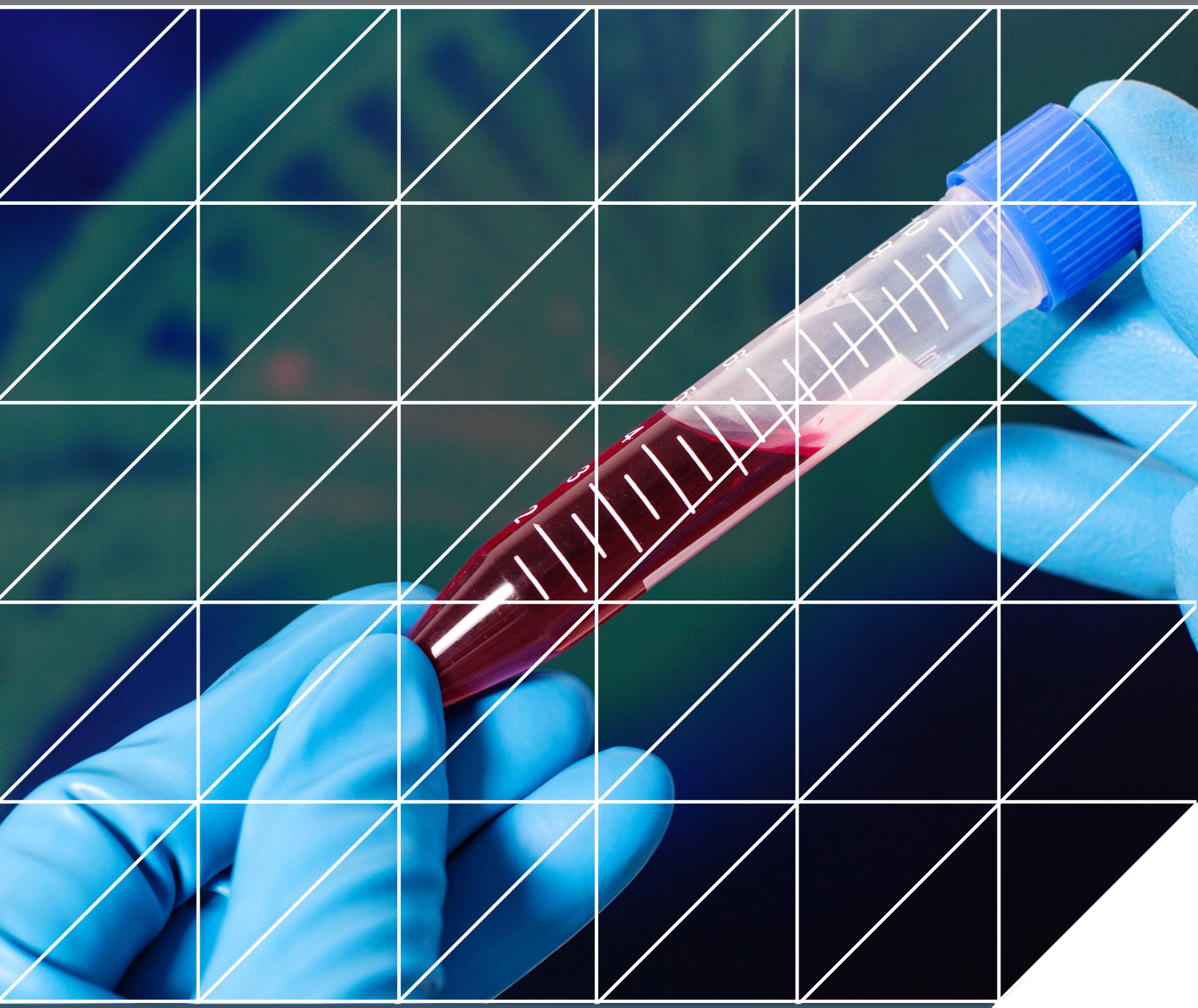

Gene Therapies in Hemophilia

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The opportunity and the challenge

Potentially curative gene therapies for hemophilia are getting closer to market, representing a transformation in care for many thousands of patients. But all is not so simple, and the fact that these gene therapies could positively impact so many people presents a new challenge for the growing impact of advanced therapies. So far, gene therapies have targeted smaller, rare, or ultra-rare indications with a high disease burden, which means access stakeholders have been more forgiving on the evidence requirements, and the high treatment costs haven't had major impacts on budgets.

But hemophilia is not as rare, and there are multiple gene therapies in development. This would result in a high budget impact, and, in these days of restricted affordability, patient access is not assured if manufacturers' target-price benchmarks are set by the previously mentioned gene therapies. Indeed, Peter Bach, a vocal proponent of US drug pricing reform has called the proposed $3 million treatment costs "just outrageous." What can be done about it?

We convened a panel of experts to find out. Ironically, on the morning of the discussion, the US Food and Drug Administration issued a Complete Response Letter to BioMarin citing durability concerns for its hemophilia gene therapy and the need to generate additional data—something the panel would debate in a more general context.

Jeremy Schafer, Head of US Payer Value, Strategy, and Innovation at UCB, started the discussion off on how to think about price. "So much of the promise of these therapies is in the long-term value—the idea that the patient will be cured of their need for ongoing treatments or procedures that their condition requires," he said. "It's a matter of assessing what those cost offsets are and what time horizon you look at.

"Taking a counter-example of the recently approved gene therapy for a form of blindness, a cure has a tremendous impact for the patient, but it doesn't save any money for the payer. On the other side, manufacturers of gene therapies for hemophilia have an opportunity because patients are currently on therapies that can cost hundreds of thousands of dollars per year. A manufacturer can say that over 5 years that patient is going to cost you $1 million dollars, so pay that up front and be done with it.

"Naturally, some US payers will want to see that return on investment within 2 to 3 years, and while that's probably not realistic for manufacturers, it helps them to at least understand the mindset of payers."

In Europe, ***Oriol Sola-Morales, Professor of Health Economics, former Spanish payer, and a founding member of the European Network for Health Technology Assessment (EUnetHTA)***, reminded us of the story of Glybera. "The therapy was for a very rare lipid disorder, but the market was not prepared and only Germany reimbursed it and, even then, for just a single patient," he said. "It was a commercial failure.

"But the market is evolving, and payers have become more aware of these therapies, and, as of now, we have 4 conditionally approved therapies, if you include both cell and gene therapies. Given the small populations and that some of these were almost last-resort treatments, payers were willing to take these on, but as we move onto not-so-rare diseases, they will look again."

Former provincial payer in Canada, Olaf Koester, who was also the co-chair of the pan-Canadian Oncology Drug Review (pCODR) and a founding member of the pan-Canadian

Pharmaceutical Alliance (pCPA), emphasized the broader problem. “There are more than 150 late-stage investigational cell and gene therapies, and if just 10 to 20 come to market in the next few years, we need to think about what that does to a payer and whether the current system is sustainable,” he said. “These therapies are expected to provide considerable benefit to patients, but we’ve seen with the latest treatments for hepatitis C, for example, that there is a pricing and access risk of having a large population with a high upfront cost.

“Rare disease treatment is no longer rare, and there are countless rare diseases that don’t yet have treatments, but as they come to fruition, it will be a case of balancing innovation and investment. It will put stress and strain on the system for all nations around the globe.”

According to Jeremy, “Payers in the US will be concerned about a land rush, but is everyone with hemophilia going to want gene therapy? Probably not, because some are well controlled, but insurers with a disproportionate number of patients will take a hit. While some payers are likely to follow the label, others may ration to last line only.”

“Or they’ll adopt more stringent clinical reimbursement criteria and target patients who can benefit most, perhaps the younger ones or those with more severe disease. In effect, the payer makes the condition rare by focusing on a smaller number of patients,” Oriol added. “The cell therapies have been successful in part because they were felt as a true revolution in care and a life-changing treatment. But in hemophilia, it is not a paradigm shift. Patients are on treatment that works pretty well. Maybe it’s inconvenient for them, but if they are receiving treatment, they are typically well. That’s the payer perception anyway.”

The value conundrum

Olaf believes that much of the problem comes down to limitations in the clinical proof of the value of the treatment. “A lot of the clinical trials for cell and gene therapies have been single-arm trials, but that is going to change,” he said. “Only in very limited situations will this be acceptable. Manufacturers need to appreciate that payers are well versed in hemophilia, all the way from plasma to emicizumab. They know what they’re paying and what they’re paying for. Single-arm trials will particularly be challenged with the competition in this area; payers want robust evidence.”

Jeremy added that the uncertainty of the benefit over the long term is a compounding issue: “Durability will be key. As well as being a clinical question for the regulators, it plays into the cost-effectiveness assessment for payers who are going to ask if they use it, are they free of these high costs forever, or after 3 to 4 years, will patients have some breakthrough therapy requirements and then 6 to 7 years beyond that will they need chronic therapy all over again, which negates the point of treatment.”

Audience poll

What will be the most important factor in the prices of gene therapies for hemophilia in 5 years?

75%
DURABILITY OF EFFECT

12.5%
COST-EFFECTIVENESS

12.5%
COMPETITION

Clearly being able to prove benefit over the long term is important, but this can lead to a "chicken and egg" situation because on one side you have the request for longer-term data and on the other you have payers delaying reimbursement and access to patients who might help generate this data. But what is the right level of evidence?

Oriol offered some further considerations for manufacturers: "There is a lot of focus on how to develop the value once the product is on the market and how to sustain the value, but manufacturers have to capture the initial value, too. On a number of occasions, manufacturers fail to understand the features of the market, which is, what is the true epidemiology? Often, they say it's a rare disease, and they don't know the numbers, but then the payer can say, we don't know if we want to pay.

"You also need to move to thinking about value all the way from the therapeutic area level to a system-wide and societal perspective. That means, firstly, thinking about treatment options and sequencing. Do we stop a treatment that is working for a gene therapy in the hopes that we never need it again? Or do we wait until a certain time, such as when the treatment becomes less effective? Or, if I stop an effective treatment, can I reintroduce it, or is there immunity? Manufacturers need to make it clear to payers that there are alternative treatments in this case, otherwise their product will immediately be put to last line.

"Then you have the situation where the gene therapy is an additive therapy. It is not perfect, and the patient requires some top-up of factor replacement therapies. How do you reflect that in the value and pricing assessment? It is not as simple as a linear equation of 'I'm saving this much over 10 years, so I'll charge this amount.' It is much more nuanced and complicated.

"Related to this is understanding the real patient flow. For example, when novel oral anticoagulants were introduced, one of the major problems was, what do we do with all the hematologists who have previously controlled these patients? How does the system change? What do I do with the physicians treating hemophilia now—retrain, retire? You have to come with a plan.

"Finally, and more broadly, you have to think about whether society is willing to pay all that money for a limited patient population."

The future of payment

"The approach to paying for cell and gene therapies in the US is quite fragmented, with the market trying to grapple with and best understand what to do with these therapies and how to overcome some of the barriers, which are pretty considerable," said Jeremy. "These include the fact that, in the commercial setting, members don't necessarily stay with their plans for more than a couple of years, which makes the large upfront investment associated with gene therapies worrying for the insurer paying out."

As Olaf noted, this would be even worse if some health insurers have a free-rider policy in order to avoid any treatment costs. But Jeremy hopes it will start to balance out: "As the market matures, it will be less concerning because, yes, an insurer may be at risk of paying for a treatment and then a patient leaving, but it would also potentially have a patient move to it that had the treatment paid for by another insurer.

"For the moment, we have seen lots of prior authorization medical policies on the appropriate patients for gene therapies, and we've even seen some healthcare plans do a benefit exclusion and not cover them. But, beyond that, contracting and reimbursement seem to be in start-up mode, and we're a little further behind Europe."

Potential solutions to the high upfront costs include outcomes-based payments and staggered "annuity" installments as well as a combination of the two. According to Jeremy, "We are seeing outcomes-based agreements bubbling up to the top in the US, as payers have experience in hemophilia where you can look at specific things like bleeds and breakthrough therapy, and it's easy to do an outcomes-based agreement. Maybe the gene therapy manufacturer can even cover those additional treatment costs as part of the risk share.

"This is especially so as we are also moving into a data-rich area. But we need to have a lot of the health economic value clarified up front, as well as plan for building real-world evidence. Imagine how impactful it will be to prove the savings produced after the treatment from beforehand in the same cohort of patients in claims data. The data and costs are very easy to track."

Olaf reflected that this doesn't solve all problems: "When we speak about hemophilia, which has a high cost per patient, we should also consider long-term budget impact and affordability over time." Oriol agreed: "There will also be a discount based on the numbers. One of the things you fear most as a payer is the sliding increase in patients without the label changing, based on the perceived success of the treatment. A budget cap of some kind would help mitigate that."

On staggered installments, Olaf thinks, "They could work from an individual perspective; that is true. But when you have hundreds or thousands of patients, after 5 years, you are paying a lot of money. From an accounting perspective, it doesn't work, so we have to be smarter."

Audience poll

What type of payment approach is most sustainable for payers?

61%
MIX

30%
OUTCOMES

4%
UP FRONT

4%
ANNUITY

In the US, there are also issues. Jeremy says "With an annuity payment, if a patient wants to switch insurance provider, they might face difficulties if the treatment isn't covered by stricter prior authorization criteria of the insurer they want to switch to.

"But there are alternative funding and payment models. Reinsurance offerings like the EMBARC program for gene therapies help to mitigate risk, but they don't really have anything to do with value."

Still, Olaf thinks payers will have to look at other investment structures: "Smaller insurers might particularly want to explore things like structured bonds, where you hedge risk through derivatives or supply a credit through a third-party finance company, or even a tradeable warranty program, which allows you to address the risk.

"This is especially important given the COVID-19 situation where healthcare resources and funds will be depleted, so payers are going to need some way of rebalancing their books. All stakeholders need to consider a larger macro perspective, because the current systems are not yet adequate to provide these assessments or implement the contracts.

"Combinations of these are all part of the bargaining process, and there is not a one-size-fits-all approach across the globe, because different countries have varying levels of affordability and capability."

Oriol agreed: "For most countries, if a gene therapy is $1 million and there are 10 new treatments per year, in a few years that sum will be unaffordable. The solution is either not accepting or discounting. We need to find a solution, because the prices are not sustainable."

What now?

Sustainability is one key word here, because solutions to these challenges must be effective over the long term. In hemophilia, and more broadly, manufacturers need to get a handle on the budget impact of their therapies and explore pragmatic payment models that consider both costs and clinical outcomes, all in the wider context of affordability and ongoing health system change.

But they'll also need to think about the basics of targeting the appropriate patients and bringing the most robust data possible, while being transparent and adaptable with how they plan to address durability concerns, which also includes how they price their products. Ultimately, it will take collaboration to avoid unnecessary delays and restrictions to access for patients who can benefit from these innovations. We look forward to seeing how discussion moves to action.

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