Sarah Emond:
What's so fascinating about cell and gene therapy is we might actually be starting to be able to use that cure word and have the underlying reason that you have hemophilia, you have sickle cell disease, be treated with this one-time therapy and it's a very different place to be in than taking a chronic therapy for the rest of your life.

Ellen Kelsay:
That's Sarah Emond, president-elect of the Institute for Clinical and Economic Review, commonly referred to as ICER. ICER's goal is to evaluate the clinical and economic value of medical treatments and technologies to promote fair pricing and better access to effective health care. Sarah joined ICER almost 15 years ago as its first chief operating officer and has been an integral part of the organization's development and impact. She joins us to talk about one of the fastest growing areas of pharmaceutical research, investment and life-saving potential, cell and gene therapies.

I'm Ellen Kelsey and this is a Business Group on Health podcast, conversations with experts on the most relevant health and well-being issues facing employers.

Today, Sarah shares insights from ICER's research on the growth of cell and gene therapies and ways to finance these high-cost drugs. In the next 10 years, the supply of cell and gene therapies is projected to quadruple. These numbers are more than just data; they reflect a shift in medicine toward potentially curative therapies.

Sarah, we're thrilled to have you on the podcast today.

Sarah Emond:
It's such a pleasure to be here, Ellen. Thank you.

Ellen Kelsay:
All right and this is a really interesting topic that I'm excited to bring to our audience and you certainly have a unique and very well-informed perspective on it. Let's dive right in. Can you describe, in layperson's terms, what are cell and gene therapies?

Sarah Emond:
That’s such a great question. They get talked about a lot, but I don't think there's a lot of understanding of what we're actually talking about. It's fun to think about where we've come from to get to this point, because we've been in the health care industry for a couple of decades and I remember when we were sequencing the human genome and we were all so excited to see what was going to happen with that, and here we are actually seeing what comes from that kind of amazing innovation in science. We now have the ability to deliver therapies into people that can help fix genetic mistakes that cause illness. So if we're talking about cell and gene therapies, we're talking about a category of interventions that actually deliver healthy working genes to help replace genes that weren't working correctly in individuals. For a gene therapy, that might mean we're going to have a new line of cells that can produce factor. A factor is something that is missing or in very low amounts in people with a bleeding disorder called hemophilia. We might be talking about a cell therapy where we actually take cells out of a person, engineer those cells to become basically an army to fight cancer, and we put those cells back into a person and they can go and target cancer cells, destroy the cancer cells without destroying other healthy cells, which many of us have experienced in our families as a side effect of some of the current treatments for cancer. So cell and gene therapies are a category of treatment that are meant to be one-time interventions to cure, potentially cure, very serious disease.

Ellen Kelsay:
Alright, we're going to come back to that one-time intervention part in just a minute, but I think you just answered this. So how are they different from typical medical treatments? It sounds like it's actually taking the cell, taking the gene, re-engineering, retooling them, and then reinserting them back into the individual to combat and treat the disease. That is different than other traditional medications. In what other ways, again, layperson's term, how would you describe these from other traditional medications?

Sarah Emond:
I think the big difference is to think about treating the root of a disease versus treating the symptoms of a disease. A lot of the therapies that we've developed, and there's been amazing innovation in spaces like rheumatoid arthritis and Crohn's disease, those therapies treat the symptoms of the disease or treat some part of the condition to help alleviate symptoms, but it doesn't cure you of the underlying disease that you have. What's so fascinating about cell and gene therapy is we might actually be starting to be able to use that cure word and have the underlying reason that you have hemophilia, you have sickle cell disease, be treated with this one-time therapy and it's a very different place to be in than taking a chronic therapy for the rest of your life. That's the big distinction. Also I know we'll talk a little bit about the payment piece of this because we're not talking about something that you're paying for every month for the rest of somebody's life. We're talking about paying one time for something that's trying to address and cure the underlying disease.

Ellen Kelsay:
Super helpful. You just mentioned a couple, sickle cell, hemophilia, what other diseases/conditions are typically associated with cell and gene therapy treatments?

Sarah Emond:
Yes, on the cell therapy side, we've had a lot of amazing innovation in the blood cancer space. This is the idea you can take cells from somebody, modify them, put them back into the body and they can target and treat the cancer cells circulating in your blood - think leukemia, lymphoma. On the cell side, we see a lot of innovation happening in very rare conditions like Duchenne muscular dystrophy, a particular type of inherited blindness, which was actually the first gene therapy approved in the United States, and we have that sort of being the first foray. What's really interesting and they're years away is are we going to see some of these cell and gene therapies addressing more common conditions? I heard recently about something in development for treating high cholesterol, something in development for macular degeneration. These are very common conditions and if we are able to fix the sort of genetic underpinnings of what creates these conditions, we're going to have a whole other conversation about what that means for a health system trying to pay for these sometimes very expensive therapies for common conditions.

Ellen Kelsay:
Okay. You're doing such a nice job of setting the stage for so many topics I want to delve into with you. For many of the ones that you just mentioned, these are very, very sick patients with very complex conditions for whom these therapies truly could be life-changing if not life-saving. Is that correct?

Sarah Emond:
It is. One of the examples that will stay with me for my entire career is a review that we did at ICER for spinal muscular atrophy, a condition in its most severe form that leads children to die by the age of two. The advent of a gene therapy that again went and corrected the underlying genetic cause for this muscle wasting disease is transforming lives. These children are thriving and hitting milestones of any other kid. I heard a story when we did this review of a family, they had lost their son to spinal muscular atrophy and the advent of the gene therapy actually gave them the courage to try to have children again. It's that kind of transformational innovation that really does at moments have me with my jaw slack. I am just amazed at what we're able to do. So the promise of leveraging what we've learned by sequencing the human genome, by understanding how genetic defects lead to certain diseases, and what we can do now that we have the technology to address those is kind of mind blowing.

Ellen Kelsay:
It is unbelievable innovation in this space for sure. If you could maybe give us a little bit of a walk back in time in the history of cell gene therapies, FDA approvals, anything that would be notable that you'd want to call out of how we even got to this place of having these therapies available.

Sarah Emond:
Well, there's been several policy choices that we've made over the years that have set the groundwork for being able to have this type of innovation. It's not just on the science side. One of them is the Orphan Drug Act, which was a policy passed by Congress that said, hey, there's not a lot of incentive right now for for-profit biopharmaceutical companies to develop drugs for conditions that only impact a few people because in that case, they might not think that they can recoup their investment, because there's such a small population. And the Orphan Drug Act helped spur innovation in the area of treatments for rare conditions by saying, here are some policy levers we can pull to make that easier, whether it's research and development credits or more interactions with the FDA to make sure you're developing the research program correctly in a way that was most likely to lead to approval has really been transformational for people with rare conditions. We still have a long way to go. There's something like 5,000 different rare conditions and we only have a fraction of them that have effective treatments, but that's one sort of policy choice that we made to incentivize and accelerate innovation in that space. The other is related, which is the accelerated approval pathway. This is a pathway that was developed to say, hey, instead of only judging whether a drug works on what we call a hard endpoint like a clinical outcome, did it prevent heart attacks and strokes? Did it lead to fewer bleeds? If you're a patient with hemophilia, accelerated approval says for some very serious conditions, we're okay with what we'll call a surrogate outcome. So instead of waiting for the results of whether or not heart attacks and strokes are prevented, we'll say lowering LDL, the bad cholesterol, is an okay marker to get approval or raising the amount of factor, that's the blood clotting agent patients in hemophilia need, raising that is okay, and maybe we don't need data on the amount of bleeding or long-term outcomes that it prevents. What that did, the accelerated approval pathway, was really helped get more drugs approved for serious conditions to more patients faster. Now, importantly with accelerated approval, the social contract, if you will, was that those manufacturers then needed to do additional trials to make sure that the drugs actually worked and they weren't only working on that surrogate outcome. We've had mixed results about how often industry is holding up that end of the bargain. We do have examples where things were approved under accelerated approval that ultimately didn't show benefit to patients. So we need to make sure that when we're talking about these pathways and how we're getting to these amazing innovations in cell and gene therapies, but that we also have the ability to know whether or not they work. I would say from an industry perspective, an FDA regulatory perspective, we've laid the groundwork to be able to get these cell and gene therapies to patients, but we also have a commitment and a responsibility to make sure we get that long-term data to know how they're ultimately helping patients.

Ellen Kelsay:
That's really helpful, thank you. You've alluded to some of these earlier, but let's go through for all of the unbelievable promise, potential and benefit that comes with these therapies, there are also some challenges. Let's go through what some of those are. You mentioned cost and you just mentioned kind of long-term effectiveness. Let's elaborate on what else would you add to that list of potential challenges.

Sarah Emond:
Unlike some of the other therapies in our system, whether it's what we'll call a small molecule, this is a drug that through chemistry you can basically make in a lab or even a biologic, which is something that is grown in cells, extracted and then often infused into people, we have made, especially in the small molecule side, a lot of innovation on the manufacturing and how efficient we can do that. Even on the biologic side, it is more difficult and more expensive to develop a biologic, but even on that manufacturing side, we've been able to make really good progress. What's interesting about the cell and gene therapy space is because it's so new, we're still in a place where we need to learn efficiencies and get some additional ability to manufacture these things more easily. Now, there will be a rate limiting step here, because if it's a cell therapy like we were talking about, that's actually taking cells from somebody, engineering them and putting them back in. We

might on the margins get a little bit better or more efficient at doing that, but that's a very complicated medical procedure to manufacture those cells. On the gene therapy side, because often gene therapies are using a vector, usually a virus, not a harmful one, to then deliver the new genetic code, that's a pretty complicated process for doing that type of work. So right from the start, depending on how you think about pricing, if you think about it, if you are a for-profit company, you need to be able to charge at least enough to recoup the cost of making the drug, not to mention all the costs of doing the research and the development and getting through FDA approval. And that's an area where I don't think we're having that conversation enough going, okay, these things are difficult to manufacture and expensive, and so how do we think about that when we think about the challenges of developing more cell and gene therapies, especially if we want to think about doing so in a way that's affordable for the health care system.

Ellen Kelsay:
That's a big one. For patients, for any payer of these services, that is a considerable one, especially as you referenced earlier that some of these might be for more common conditions that will theoretically impact a larger swath of the population.

Sarah Emond:
That's right and that's where we need to be doing our very best as a health care system of not doing it the way we've always done it. We need to be talking with all of the different stakeholders, having honest conversations about budgets and trade-offs and long-term value, instead of what has gotten us here to this point, which is maybe picking the highest price you think you can, and then a payer system that might say, well, I'm going to make it really hard to get through some coverage policy choices, and then ultimately nothing but frustration for patients and their physicians trying to get access to some of these therapies. If there's any call to arms of this conversation today, it’s we have to kind of leave the status quo behind when we think about paying for and making these new therapies accessible for patients.

Ellen Kelsay:
When you talk about accessibility, it's not just the cost. Are there other things that you would call out from an accessibility perspective? Are physicians well-informed? Do they know when to use these therapies? Are there other issues related to accessibility from a manufacturer supply side, health equity access? What else would you call out around accessibility?

Sarah Emond:
The health equity one for me is top of mind. With a lot of these interventions, whether it's a cell therapy or a gene therapy, you're talking about them being delivered at centers of excellence, at academic medical centers. That's where we have the expertise. They've been involved in the clinical trials, they have the infrastructure for actually delivering the therapy, they have the expertise in knowing how to do so safely and how to do monitoring. And we know that there are significant challenges when therapies are only available at academic medical centers, whether it's rural populations, people who don't have access to the academic medical centers for a number of reasons. We really need to make sure that we have a system that's not just saying, okay, yes, I'm going to cover this new gene therapy, but it's also how are we paying for a complete support of that patient to access the therapy? The other thing that's interesting about some of these regimens, and this is the case for the therapies that are nearing approval for sickle cell disease, is there is a pretty intense conditioning regimen before you can even get the gene therapy, akin to chemotherapy or a bone marrow transplant. So intensive treatment, needing to be in the hospital for a fair amount of time, risk of infection that comes with that, and that's even before you get the therapy itself. So you want to make sure that we've got a clinical team that is versed in that, knows how to handle that to make sure we can limit as many complications as we can. The accessibility piece in terms of the number of places where we'll be able to get these gene therapies is top of mind. And one other point on sickle cell, if I may, the other thing that we are really good at in the U.S. when we talk about these issues is to only think about the United States. If we're thinking about something like a potentially curative therapy for sickle cell disease to not also be having a conversation about how we're ensuring access in Africa where the most people live with sickle cell disease, then we're sort of missing the

point. I don't know that we've done enough work yet to think about the infrastructure needed and also the resources needed to get the gene therapies once they're approved to patients who need them in Africa.

Ellen Kelsay:
I'm speaking with Sarah Emond about the latest advancements in cell and gene therapy and their impact on employees' lives.

DayTwo:
In the United States, 1 in 10 adults have type 2 diabetes and 1 in 3 adults are overweight. DayTwo believes that with the right knowledge about your personal biology, food can easily be used for meaningful and sustainable clinical impact. Using gut microbiome profiling and machine learning algorithms to predict blood sugar response to foods, DayTwo empowers members through an easy-to-use digital platform to make small, highly personalized tweaks to their nutrition plans. This garners significant results including weight loss, A1C reduction, improvement in energy levels and sleep quality and reduction or elimination of prescription medications. Instead of removing certain foods from an individual's diet altogether, DayTwo's proprietary algorithm suggests food combinations that are unique to the member's microbiome makeup, taking the stress out of food choices. To learn more, go to www.daytwo.com or email us at contact@daytwo.com.

Ellen Kelsay:
You mentioned long-term studies. Is there anything around the safety of these drugs that is still a question mark to be determined? I don't want to cast any doubt that these aren't worthy worthwhile drugs, but we just don't have a long enough study horizon yet to look back on and say for sure these are one-time interventions, these are potentially curative. So anything around the safety side of things or the effectiveness side of things that you would call out?

Sarah Emond:
I think you've hit on two of the biggest questions that we face as we see more and more gene therapies get approved. On the safety side, we've got data for some of these gene therapies, 5 years now approaching 10 years, and there are some signals that we're watching and they do differ by therapy, but generally we're seeing a pretty good safety profile. But again, we've got 5, 10 years. Kind of a cousin to safety for me is that we don't know a lot about what happens if you need another gene therapy. If you use the typical vector, there's a very common vector, AAV that's used for delivering gene therapies, there's a school of thought that says you're actually not able to ever get another AAV therapy again, because your body has developed antibodies to the virus that delivered the gene therapy. That's sort of adjacent to safety and just thinking about what it means to make a decision to deliver a gene therapy at a certain point when there might be better therapies that are coming down the line. But the second and the second cousin to that is that we also don't know a lot about the durability of effect. There was talk about the spinal muscular atrophy gene therapy being curative and that we expected that it would be a lifetime of benefit. Interestingly, we need more data on this, but we know that there's a lot of patients who get that gene therapy who then actually start getting another therapy for spinal muscular atrophy. That's something that's a chronic therapy that they're then using a few years after they get the gene therapy. Now is that because the gene therapy was starting to wear off? Is it because we have neurologists who might just want to do a build and suspenders approach and use every available tool in the toolbox? Questions that still need answering, but given that at most we've got a decade of data for some of these gene therapies, we really do have a lot of work to do to understand the durability of the effect. Now that said, some of these therapies are still going to be “worth it” even if the duration of the benefit is only 5 years or 10 years, but that then gets into how we think about paying for them and paying for them over time in a way that can kind of protect the social investment in these while we have these unanswered questions about durability of effect.

Ellen Kelsay:
Alright, let's go to payment. What should we be thinking about? You said we need to think differently. That's the call to arms to the industry to not do it the way we've always done it, so what would you offer as alternatives when we think about financing and payment for these types of therapies?

Sarah Emond:
I think that this is an area where we need to realize that because of the uncertainty, because we don't know how long the benefit will last, but some of the pricing decisions that are being made by industry are assuming a lifetime of benefit, that we need risk-based, outcomes-based contracts for these therapies. That would mean, and they can come in different flavors, but that would basically ensure that the ultimate payer, whether it's Medicaid or a private payer or the VA has some ability to either get money back or they only pay over time for patients who meet certain clinical milestones. This would allow us to feel as though we are paying for value. If we have the ability to pay 20% of the cost over 5 years for patients with beta thalassemia, we know that if they end up needing to go back on transfusions to treat their beta thalassemia, we know that that therapy is no longer working for them and we'd either stop paying for it at that point or we'd have the ability to get some of the money that we had paid upfront back in a rebate or a refund. There are also attempts to think about pooling resources to pay for these, because if you're a medium-sized or a smaller self-insured employer, this could be a lightning strike. If your total benefit for your total spend for pharmaceuticals is a million dollars a year and then there's a child born to one of your employees who has spinal muscular atrophy and you get a bill for $2 million, that's a lightning strike. So what if that small employer was part of a larger pool of employers? So a risk pooling approach, paying a fixed amount to be part of the pool, but that means if I have a patient or an employee who needs access to one of these therapies, I'm not then paying anything additional for that gene therapy, because I've already sort of paid into the risk pool. We also know that reinsurance is a potential avenue that employers can use to basically say, if my insurance costs, my health insurance costs go above X amount, my reinsurance policy will protect me. The problem with reinsurance is we're starting to see that might be great once, but if you get then a second incidence of the same condition needing a gene therapy or a different gene therapy, you might see your reinsurance premiums go up too high and then you're back to wondering, well, how am I going to make all of this work in terms of managing my budget, but also providing access to patients?

Ellen Kelsay:
Are all of those theoretical, conceptual ideas or are you seeing any of those in practice being deployed today?

Sarah Emond:
I've actually been pretty impressed the way that the industry is leading on the outcomes-based contract side. So bluebird bio's, the manufacturer of that beta thalassemia gene therapy I mentioned, and they were very clear from the beginning that they were offering an outcomes-based contract that basically said that if any patients were back on a transfusion at 5 years, there'd be some sort of refund depending on when they went back onto the transfusions. I know that BioMarin is doing this for its hemophilia gene therapy. I think what we're hoping to see is that there is willingness on the payer side to enter these and infrastructure to support payers doing this. I'm thinking specifically about payers like Medicaid, that don't necessarily have a big staff who can adjudicate these sometimes complicated outcomes-based contracts. There is actually a proposed demonstration project from the Centers for Medicaid and Medicare Innovation (CMMI) that would say, well, hey, maybe CMMI is the organization and the place that we will sort of house and administer these outcomes-based contracts on behalf of Medicaid departments so that we don't have each state trying to build up the capacity to do it. And so there's some work being done and I am excited about some of the outcomes-based contracts that we have seen, the demonstration project from CMMI, but there's absolutely need for more innovation in this space and more attention to how we pay for these very expensive therapies in a way that doesn't break the bank.

Ellen Kelsay:
Is there anything that you could see happening, like today we have end-stage renal disease carved out federal coverage, anything that you could see potentially coming into play in this space as well?

Sarah Emond:
I think that's part of the conversation. The end-stage renal disease example is a great one and everyone just sort of said, yep, okay, it's time for this just to be a Medicare benefit. It doesn't matter how old you are, that's

how it's going to be paid for and how we're going to ensure affordable access. The idea of a federal carve-out to pay for these cell and gene therapies has been proposed. As you might imagine, there's a fair amount of resistance to this idea because of the slippery slope argument that it's going to lead to more government intervention in health care and potentially a single payer. But I also think it's a moment to say, let's at least talk about the pros and cons of that approach, because it doesn't have to be that it's a death nail for innovation. There is the possibility of the federal government being more willing to pay a value-based price and not just want a low price because they see sort of the ultimate return on investment for doing so. Just a quick side note, one of the reasons we have a lot of payers who worry about paying for these therapies is that family might leave their plan in two years and so they've made this very big upfront investment, but then it goes off to another plan to basically "reap the benefit." Now my argument to that is, well, then if someone leaves your plan, you're going to get someone in your plan whose gene therapy was paid for from somewhere else and so maybe it washes out, but you could see this federal carve out making sense if they're willing to pay the value-based price, which in often cases is millions of dollars because of the magnitude of the benefit these drugs bring. To be continued, Ellen, on whether or not we're going to see some real action on a federal carve out.

Ellen Kelsay:
Well, you and your team have a paper coming out. Let's tell the audience a little bit about that.

Sarah Emond:
We have been working on this issue for a while. There's a paper we did a couple of years ago that said, how are we going to pay for gene therapies? This was about 5 years ago. Well, it turns out we still need to be having this conversation and we're happy to be leading it with our policy leadership forum. We'll be talking about this in person in December, and then next spring, March/April timeframe, we'll be putting out a white paper that goes through all of the different options for paying for these expensive gene therapies. We'll touch on the outcomes-based contract, the reinsurance, the risk pooling, the federal carve-out. What our white papers do, the ones that we develop with the policy leadership forum, is not necessarily say this is the way we should do it. It's a menu of options that go through the pros and cons and sort of take a deep honest look at what the trade-offs would be with some of these approaches. We're excited to be working on that and we hope that it'll be useful to contribute to this conversation. Stay tuned for that next spring.

Ellen Kelsay:
We'll be eagerly awaiting it, thank you. You've mentioned already a couple considerations for payers. Knowing our audience, mostly self-funded employers, what else would you offer to them as they're considering use of these therapies within their population?

Sarah Emond:
I think from an employer perspective, I would encourage them to start from a place of excitement. Whereas some of these conditions might have meant incredibly challenging absenteeism, people dropping out of the workforce to care for a sick child, we have the ability now with some of the gene therapies to return people to full productivity, whether they're a patient or a caregiver. I would be excited if I were an employer, because I know your members are so interested in the health and well-being of their employees, not just because of the productivity, but just because they believe in them. And so that as a starting point for me is something I want and hope that the employers kind of hold and then don't necessarily panic when you see the dollar sign. You might see the dollar sign, and sure, a little bit of panic is perfectly appropriate when you see a price tag of $2.1 million, but also be thinking about the power that you have to push your partners, whether it's your payer partner, your pharmacy benefit manager, your reinsurer, to offer up products that makes sense - what makes sense for your budget, what makes sense for access. Sort of centering that access question for those conversations is something the employers can bring to these conversations that you won't necessarily hear from some of the other participants in this conversation. I would say that the employers have a lot more power in this than they might think, because they can hold all of their partners to a standard and that includes putting pressure on the manufacturer side to do risk-bearing, outcomes-based agreements, to think about value-based pricing and not just pricing it as high as you possibly can. Employers have an opportunity to really

push all of the other levers and pull the other levers in the system to do better by the ultimate goal of getting these to the patients who need them.

Ellen Kelsay:
I always like to wrap on a note of optimism and as you think about all the unbelievable potential and opportunities and advantages of these therapies, let's close out with some things that give you hope as you look to the future in this space.

Sarah Emond:
I think we're going to meet this moment. I don't always bring a lot of optimism to conversations about how we fix drug pricing and access in the U.S. health care system, but I think that the science and the magnitude of the benefit that these therapies are bringing to patients is so large that we don't have any choice but to figure out how to do this in a way that's sustainable. As I'm looking to the future, I think this is the moment where we might see people shed the sort of status quo or reverting back to the way they've always done things and not really coming to a conversation about how to maybe do this differently. That coupled with the pipeline we have of cell and gene therapies for both common and rare conditions is making me pretty pumped for the future, as long as we can all remember that at the end of the day, we really can do this in a way that's sustainable if we really center value-based pricing and access in that conversation. I'm still pretty optimistic.

Ellen Kelsay:
Sarah, that was great. Thank you for joining me today on such an important topic in a really robust and rapidly evolving field with unbelievable potential. Thanks for breaking it down for the audience and look forward to staying in touch and keeping an eye on how this evolves in the future.

Sarah Emond:
It was my absolute pleasure, Ellen. Thank you for having me.

Ellen Kelsay:
I've been speaking with Sarah Emond about the latest advancements in cell and gene therapy and their impact on employees' lives. This rich pipeline of cell and gene therapies has the potential to transform care for the over 300 million people living with a rare disease worldwide.

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