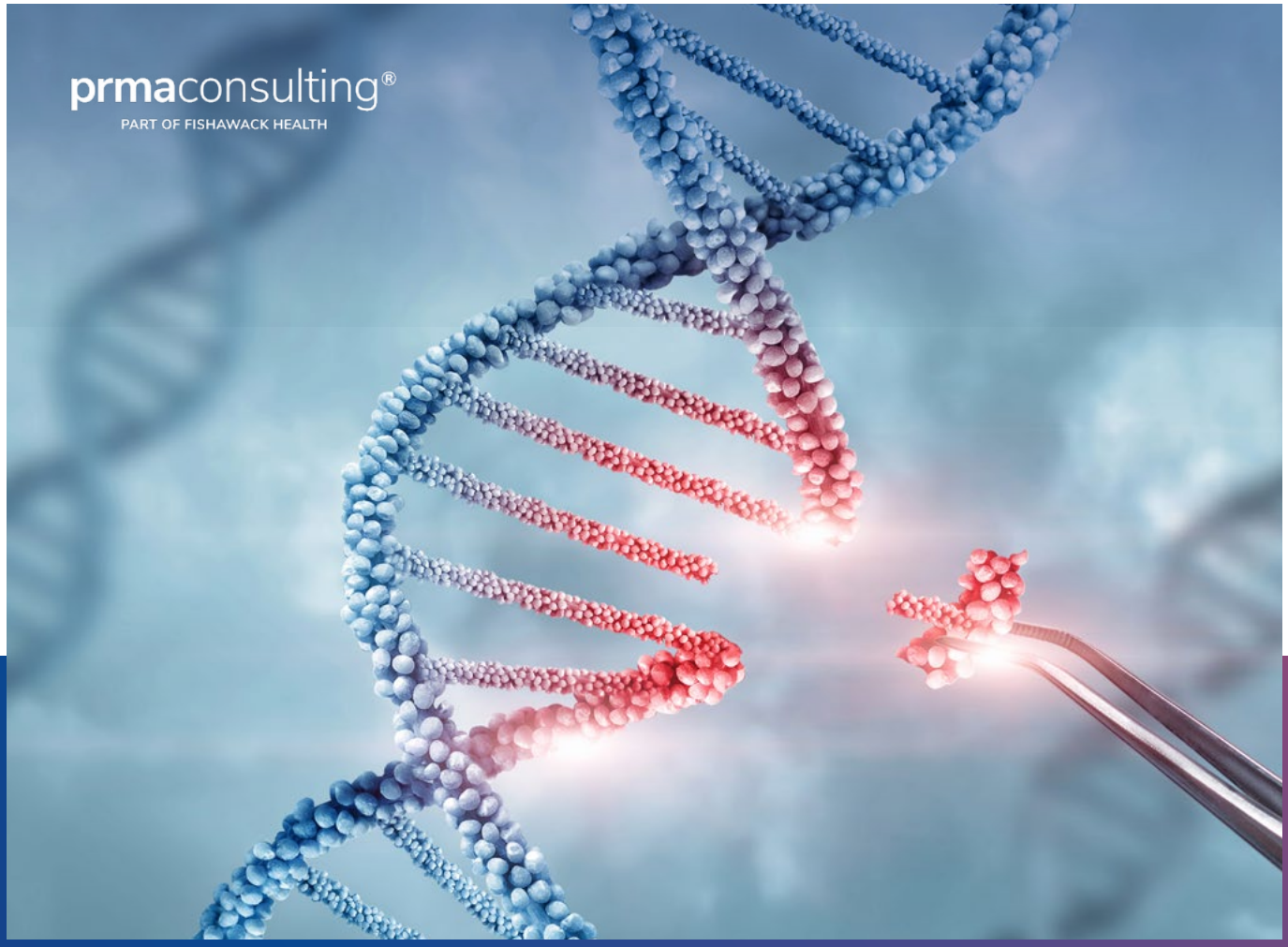


The promised land of gene therapy: commercialization of novel gene-editing technology in beta-thalassemia

With transformative treatments that leverage CRISPR gene-editing technology, there are many challenges to overcome throughout the development and patient access journey. Fishawack Health interviewed a researcher at a top-20 pharma company, multiple patients, and our own market access experts for their insights into the process, obstacles, and opportunities for biopharmaceutical companies to meet patient needs and achieve success in the market.

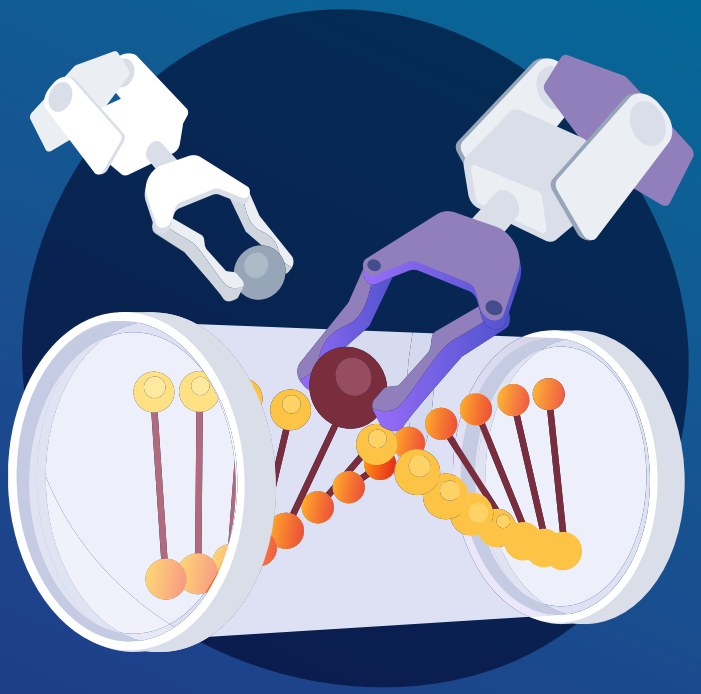
Gene therapies and associated research has grown considerably in recent years, offering more novel tools in regenerative medicine to fight disease, including rare diseases and genetic disorders. In the past decade, there has also been rapid development and interest in CRISPR/Cas9 technology and other gene-editing tools that could offer transformative treatments for patients and families affected by devastating diseases such as sickle cell disease and thalassemia.

Beta-thalassemia is a rare blood disorder caused by a genetic defect in hemoglobin. Several manufacturers are developing novel treatments for the disease, including Vertex, which has partnered with CRISPR Therapeutics to develop a gene-editing treatment for beta-thalassemia and sickle cell. In October 2022, the companies announced their plan to file exagamglogene autotemcel, the CRISPR/Cas9 gene-edited therapy, for a rolling review with the US Food and Drug Administration (FDA)[1] . Novartis also recently inked an up-to US$1.5 billion deal with Precision BioSciences to support its development of one-time treatments for beta-thalassemia and sickle cell.[2] The move marks a continuation in its ongoing commitment to exploring gene-editing technology.

Despite the surge of interest from both scientific and financial stakeholders, there remain numerous unique challenges at every step of this new frontier. From developing and financing the therapy in a timely manner to market access challenges due to the lack of maturity and extensive evidence, and explaining the complex science to physicians and patients, there are a variety of hurdles to overcome before bringing this type of technology to market. And while regenerative and curative therapies are often greatly lauded, there are also challenges in treating affected patient populations, including cost, accessibility, side effects, and other associated risks.

Earlier this year, the FDA approved the first potentially curative gene therapy to treat beta-thalassemia[3]. While multiple companies have been working to bring transformative technologies such as CRISPR to market, approval will require further consideration around the many concerns and challenges of each stakeholder at every step. From the research and development stage all the way to patient access and treatment, remaining considerate of the populations that will ultimately be the end-users and testament to the technology's success is vital.

CRISPR therapy is more precise and easier to use than other gene-editing tools and can really give the patient a better shot at a healthy life



Bringing in the patient perspective

Diagnosed with beta-thalassemia at 6 months old, Amar has had regular blood transfusions every few weeks for the majority of his life. As a child, he found himself falling behind others his age. “I always felt I was playing catch-up, through school, work, life—always making up for lost time,” he says.

“Although the technology may offer a transformative solution, it will be difficult to balance the promise with the reality of cost.”

Now in his 40s, he reflects on both the physical and mental impacts of the disease. He says, “As I’m getting older, my body is deteriorating, and it raises concerns for my future and what my life expectancy will look like. The disease has triggered other health conditions, including osteoarthritis, hypogonadism, and diabetes. It’s a constant challenge, both physically and mentally,” he says.

Zeb’s 6-year-old son is affected by thalassemia and experiences a drastic mental and physical decline after his second week post-transfusion. “His mood, his happiness, his appetite, it all shifts. And when he gets his transfusion, he is so much happier again,” Zeb says.

Patients often become quite resilient in the face of their disease, but the effects of beta-thalassemia can be fatal. And although both Zeb’s son and Amar have relied on Exjade to stave off the iron overload that comes with regular blood transfusions, both patients are constantly trying to manage their disease. “At one point, I remember I was having 18 tablets daily. When I was told my bone density was deteriorating, I was placed on bisphosphonate medication administered intravenously. I was prescribed a large dose of strong painkillers. In addition to this, I had iron chelation therapy issues, painful intramuscular testosterone injections, vitamin D tablets, and now I have the continuous glucose monitoring patch for diabetes,” says Amar.

All the individuals interviewed shared that the necessity of regular transfusions disrupted their schedules, forcing them to take time off from school, work, or holidays to maintain a healthy level of hemoglobin. With this comes the financial burden of the treatment regimen itself, plus potential extraneous expenses such as hospital fees, transportation, and parking.

Although existing treatment regimens are time intensive and have an estimated lifetime cost from US$720,000 to more than US$5 million, a curative therapy would need to be evaluated to understand the risks and costs to the patient, along with the benefits[4,5] from its price point to potential side effects, there are many reasons that might lead a patient to view the curative option as unviable. Instead, most patients endure a life-long treatment regimen involving symptom management, pain relief, and blood transfusions. CRISPR technology could offer a safer, more accessible, and life-changing method of gene therapy for these patients if the price point is set within reach.

As a one-time dose, any gene therapy for thalassemia involving CRISPR technology aims to reduce, if not eliminate, the need for blood transfusions, thereby greatly shortening the time required for treatment. This outcome would also reduce the financial burden of the disease and potentially other health issues that can occur as a result of thalassemia as well. For patients, however, there is much more to consider.

When bringing gene-editing tools to patients, biopharmaceutical companies will need to address patient needs and alleviate concerns by ensuring equitable access, healthcare professional education, sharing real-world evidence, and patient-reported outcomes to offer accurate and representative data for the patient population. On top of this, they will also need to find ways to equip patients with a comprehensive understanding of the value of the technology, side effects, risks and benefits, and other key considerations to inform their decision-making process.

A tricky balance of revenue and access

Five years on from the first gene therapy approved by the FDA, there are plenty of ongoing scientific advancements in the gene therapy space, including potentially transformative treatments in the pipeline for patients with rare diseases and limited options for treatment. This year, Bluebird Bio’s new beti-cel treatment for patients with transfusion-dependent thalassemia was approved by the FDA following its unanimous support for the one-time gene therapy earlier in the year[6].

“However, the market access challenges for regenerative medicines need to be considered alongside the opportunities they bring,” says Dr Sanjeev Gogna, Senior Director at PRMA Consulting, part of Fishawack Health. With a potential cost of up to US$3 million per dose, the newly approved beti-cel therapy is out of reach for patients without the means to afford it and challenging for healthcare systems to justify. The only other curative option for patients with beta-thalassemia thus far has been allogeneic hematopoietic stem cell transplantation (HSCT) from a matched donor, which is difficult to find. Both cost and accessibility remain primary concerns with these options.

"The complex production process and the higher acquisition cost coupled with limited or immature data also mean that, although the technology may offer a transformative solution, it will be difficult to balance the promise with the reality of cost," says Sanjeev. "The immense cost of producing a viable therapy for a small patient population necessitates setting a high price point. Biopharmaceutical companies working in this space will need to balance their profit margin with the goal of bringing curative therapy to as many patients as possible."

He says, "As this technology scales, we can anticipate major challenges to the value assessment. For any company operating in this space, it's important to understand how health technology assessment (HTA) agencies will balance the trade-off between precision, maturity of evidence, high upfront costs, and affordability, and how this relates in general to decisions over value."

"While CRISPR Therapeutics' and Vertex Pharmaceuticals' gene therapy candidate, exa-cel, also shows promise, there is still room to improve the evidence package and value presented for HTA agencies to consider it a viable option"

Generating sufficient data can be a challenge with a small patient population. HTA agencies that make decisions about potential benefit will value robust evidence to show efficacy and safety. So innovative methods for continuous monitoring of patients, accurately aligning the patients in the trial population with the treatment population, some use of real-world data, and tailoring the evidence generation plan early at the clinical phase can all help ongoing evidence-generation needs to move past approval. This also helps ensure that patients and the communities advising patients are equipped with as much data as possible to make informed decisions about their treatment options and regimen.

The late-stage clinical data presented by Bluebird Bio indicated that 89% of patients achieved transfusion independence without serious adverse side effects beyond 2 years post-infusion.[7] While CRISPR Therapeutics' and Vertex Pharmaceuticals' gene therapy candidate, exa-cel, also shows promise, there is still room to improve the evidence package and value presented for HTA agencies to consider it a viable option[6]. Sufficient evidence can also help justify the risk-benefit balance for reimbursement agencies and payer bodies, considering the therapy from a regulator perspective. "Hence, developing a strong evidence package is essential to maximize commercialization opportunities," says Sanjeev.

Building a strong foundation for ambitious ends

Gene editing opens up a world of possibilities for innovative cellular therapies that are both safe and effective, as shown in autologous CAR-T products, which have become safer as a result of gene-editing technology.

"CRISPR therapy is big for debilitating disorders that are monogenic or caused because of one gene mutation," says Manisha Padmakumar, Postdoctoral Researcher at UCB in Belgium. "It's more precise and easier to use than other gene-editing tools and can really give the patient a better shot at a healthy life."

Other methods such as lentiviral transduction can have serious side effects as it is less precise in how it places the gene of interest. Zinc-finger nucleases and TALENs have also been compared as powerful gene-editing tools but tend to involve a more painstaking process to manipulate and engineer than the Cas9 method.

"Gene therapy is very powerful, but then health insurance is still figuring out how to deal with it," says Manisha.

"For example, for most citizens in the European Union, there is heavily subsidized healthcare funded by the social security system so as to not create an economic disparity in access to health insurance. But how will they afford the millions it will take to fund this kind of one-time treatment for a single patient?"

Biopharmaceutical companies need enough profit to balance the immense investment put into this type of treatment. The higher cost of researching, developing, and producing a viable gene therapy is often passed on to patients and providers, causing difficulty in getting coverage and reimbursement for the therapy.[9] Thomas Klima, Chief Commercial Officer at Bluebird, told Endpoints News that Bluebird's approved beti-cel therapy is no longer marketed in Europe due to the lengthy pricing process and financial negotiations that payers were not ready to accept.

The high cost can put the therapy out of reach for some patients. "For companies, it's difficult to get CRISPR therapy into the pipeline at all because of the small patient population and the profit base," says Manisha. "Now, people are thinking of counter approaches that attack the problem differently, such as creating off-the-shelf therapy options, which can work for some cancers."

For some, the mindset around gene editing is focused on the risks and ethical concerns, posing a challenge for biopharmaceutical companies looking to market their product. Manisha says, "The mindset has to change. We are so used to taking off-the-shelf pills that injections initially seemed scary. Then, injections became commonplace and cell transplants were the unknown. People are still getting to a place where they accept new technology, but it will take some time."

Building the foundation of data early can help later in the pipeline, but this also requires being careful with research and development. "With social media, if even one instance doesn't produce a good result, it can have a huge social impact on people's perception, leading companies to give up gene therapy from their portfolio. Instead, there needs to be more care and expense towards research to avoid this outcome," says Manisha. "We might see an amazing result in the lab, but long-term follow-up on every clinical trial is very important, and we are seeing that more and more throughout the lifespan of the patient."

> **The healthcare provider should always have a genetic counselor or a team of geneticists.... It should ultimately be a team effort because one person cannot have all the answers or insights**

Keeping the focus on the patient first

As the healthcare landscape shifts toward a more patient-centric outlook, some companies are now working in collaboration to combine their expertise in different parts of the pipeline.[10] With this comes a shift toward greater transparency, accountability, social responsibility, and an emphasis on the value of patient lives.

With collaboration and patient outcomes in mind, Manisha says, "The healthcare provider should always have a genetic counselor or a team of geneticists if they are treating a patient with a genetic mutation. It should ultimately be a team effort because one person cannot have all the answers or insights."

> **Once the therapy is available to patients, its success in the market will hinge on whether patients make the choice to use it. Taking this into consideration, biopharmaceutical companies will need to find cost-effective ways to scale up and meet patient needs.**

Patients and caregivers are increasingly becoming advocates and experts in their own disease, more so than physicians. Including them in research and outreach to understand their disease better could be an effective way to engage the patient communities and needs earlier in the pipeline, build a stronger case for the treatment based on those insights, generate data throughout the process, and work to actively change the public perception of gene therapy with robust evidence and education.

"I look into how much testing has gone into it, how long the trials have been going on for, the potential side effects, and weigh those against the benefits," explains Amar.

This information needs to be clearly conveyed and to focus on specific areas. For example, information that helps manage expectations around the novel and complex treatment journey could be invaluable for patients considering the life-altering treatment.

Sharing real patient stories and other useful information alongside this type of content, and doing so using a variety of channels to reach all the relevant communities, could go a long way to building a more comprehensive understanding of the new technology.

This includes taking a robust approach to educate and engage healthcare professionals. Zeb says, "The information my wife and I get is mostly from conferences or online. My wife is quite proactive, so we research what's available. We were expecting more information from our consultants but found they didn't know much more than us."

Educating the healthcare professionals involved in the care of patients with rare diseases is difficult but necessary as they are integral to improving patient outcomes and advising patients and their communities to make the best decisions for the patient's short- and long-term health.

Consultants are the medical experts liaising with and helping patients make the right decisions for their treatment journey. They need to be able to convey information accurately and clearly, without the use of medical jargon. In some cases, this may include finding an individual or advocacy group to help break down the medical jargon and language. This extra step helps ensure patients, regardless of language or cultural background, are fully informed about their options. Without the relevant information and understanding, patients may not be open to alternate treatment options such as novel gene therapies.

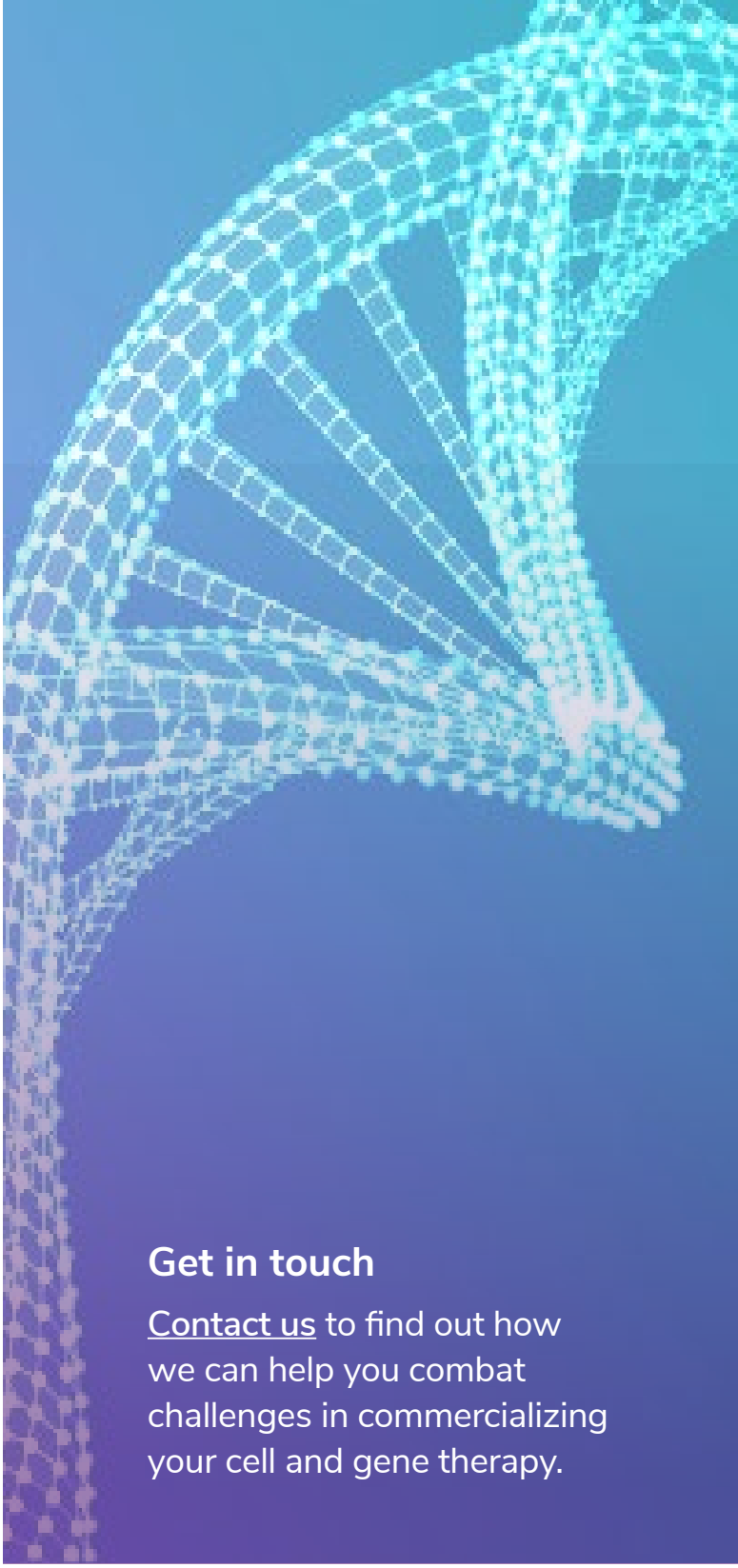
A connected approach to commercialization

With this exciting new technology in the pipeline, it is vital to take the full lifecycle into consideration, thinking about the patient experience upfront and implementing a connected approach from the start.

From competitive market analysis, first-to-market strategy, and gene delivery, to patient identification and post-treatment planning, Fishawack Health offers a wide breadth of experience and services in the rare disease and regenerative medicines space for gene therapies. With the goal of developing a sustainable business model that keeps all stakeholders in mind at every stage, we offer our integrated services to support our clients' needs wherever they are in their commercialization journey.

While many companies are not yet ready to begin the commercialization process, there is still enormous potential for strategic input. In particular, keeping the end in mind and working with a multidisciplinary view is crucial to success as the applications of CRISPR-based gene editing for revolutionizing the treatment options and experience for rare and inherited diseases grow. Ultimately, translating the value of the treatment and process in a way that overcomes both the fear of the unknown and the perceived cost burden will be of great value as more treatments are made available.

Our expertise in this area spans over 150 projects completed in the past 5 years, including projects in CAR-T, gene therapies, and rare diseases, along with working with companies across the spectrum, from emerging biotechs to top-20 pharmaceutical companies. With unique obstacles and opportunities at every step with CRISPR-based gene editing, companies in this space will need to take care in how they approach the market and position their CRISPR-based therapy to all stakeholders at each step of the commercialization process.



Get in touch

Contact us to find out how we can help you combat challenges in commercializing your cell and gene therapy.

References

1. Vertex and CRISPR Therapeutics announce global exa-cel regulatory submissions for sickle cell disease and beta thalassemia in 2022. News release. Business Wire. September 27, 2022. Accessed October 2022.
2. Philippidis A.
3. Brennan Z.
4. Weidlich D, et *al. Transfusion.* 2016;56(5):1038-1045.
5. Udeze C., et *al. HemaSphere.* 2022;6:2208-2209.
6. Keown A.
7. betibeglogene autotemcel (beti-cel) one-time gene therapy for β-thalassemia continues to demonstrate durable efficacy across pediatric and adult patient populations and all genotypes in data presented at EHA2021 virtual. News release. Bluebird Bio. June 11, 2022.
8. O'Hanlon Cohrt K.
9. Jena AB, et *al.*
10. Myers R, et *al.*