Comprehensive Care Sustainability Collaborative
National Bleeding Disorders Foundation

CCSC Briefing Document:
Gene Therapy

Hemophilia Gene Therapy Coverage, Access, and Utilization:

Current Perspectives for Health Care Stakeholders

About CCSC

Now in its tenth year, the Comprehensive Care Sustainability Collaborative (CCSC) initiative was founded by the National Bleeding Disorders Foundation (NBDF) to support the sustainability of the integrated comprehensive model of care and strives for improved patient access. CCSC has sought to achieve this aim by facilitating value-based dialogue and payer/provider collaboration. A collaborative working relationship and mutual understanding among all stakeholders is needed now more than ever considering a rapidly changing therapeutic landscape.

Available treatments for hemophilia have evolved substantially over the past 40 years, culminating in the availability of the first non-factor therapy in 2016 and the first gene therapy for hemophilia A in 2023 and the first gene therapies for hemophilia B in 2022 and 2024.[1,2,3,4] Although these recent entries to the market represent an improvement in the therapeutic space, further advancement is expected in the near future, with several other gene therapies and non-factor products in various stages of development. Gene therapy represents a long-awaited promise from a clinical perspective, but it does not diminish the role of factor replacement therapy or the importance of hemophilia treatment centers (HTCs) in patient management. As the first patients have begun to receive commercially available gene therapies, it is vital to establish a standardized model of care. HTCs are poised to remain at the center of gene therapy administration and post-administration follow-up care and data collection.

Leaders from the National Bleeding Disorders Foundation (NBDF), Hemophilia Alliance, and faculty advisors from the Comprehensive Care Sustainability Collaborative (CCSC) discussed these and other considerations in January 2024, encompassing the initial uptake of gene therapy, administration and follow-up protocols, institutional readiness, and challenges faced by patients and health care providers. These stakeholders represented the medical, research, and patient advocacy communities. Emerging themes from their discussions included the transformative potential of gene therapy, access issues, and the need for comprehensive patient support and education. The conversation outlined considerations regarding the effectiveness, side effects, and long-term outcomes of gene therapy, comparing it to existing treatments and potential future alternatives. The dialogue also highlighted the importance of collaborative efforts among stakeholders to ensure equitable coverage, address barriers to access, and support optimal care via the HTC integrated comprehensive care model.

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Current Utilization of Commercially Available Gene Therapy Products

Although the current demographic of individuals deemed eligible for gene therapy according to pivotal trial inclusion criteria represents only a fraction of the total population of people with hemophilia, the leaders acknowledged that the uptake and utilization of commercially available products has been generally slower than anticipated. In June 2023, the first patient received treatment with gene therapy, but the NBDF, Hemophilia Alliance, and CCSC leaders were not aware of utilization beyond the few initial publicized administrations.[5]

> "I ask patients, 'What's preventing you from moving forward with gene therapy?' And a consistent answer I get is they really can't afford it. Taking income into consideration, even with health insurance, patients can't imagine covering a 20% share in coinsurance."
>
> - NBDF Representative

> "The flow of claims has caused some issues with gene therapy utilization, and it's taking a little longer for that claim to get pushed through."
>
> - Hemophilia Alliance Representative

The limited initial uptake of gene therapy came as a surprise to many payer and industry stakeholders. Survey data fielded before the gene therapies were approved showed that most patients were "willing" or "very willing" to undergo treatment with gene therapy.[6] Patients report that normalization of bleeding and the frequency and durability of treatment are the two most important attributes of gene therapies over available treatments.[7] However, the stakeholders shared that lower-than-expected initial utilization of gene therapies in bleeding disorders is likely due to a limited segment of eligible patients, concerns regarding the cost of gene therapy, available treatment options already on the market, and additional promising therapies in the pipeline (including next-generation hemophilia gene therapies). The stakeholders identified additional delays that may be impacting the update of gene therapies, such as payer processes of setting prior authorization (PA) criteria, establishing contracted rates, and claims review and approval. Unlike previously listed barriers to gene therapy utilization, such delays related to claims approval and payment processes are expected to decrease in the future.

The Role of the HTC in Administration and Follow-Up

Most administrations of commercially available hemophilia gene therapy to date have taken place in the HTC setting, with the stakeholders noting that administration often took place at centers that were involved in the clinical trial phase of development. According to NBDF and Hemophilia Alliance representatives, gene therapies are purchased directly through a commercial specialty pharmacy at a non-340B price so that the HTC or parent institution does not have to take on the financial risk. Although stakeholders reported the administration of gene therapy for hemophilia B administered in non-HTC settings, it was reiterated by all of the experts that maintaining HTC involvement in the process is crucial, specifically in the follow-up of patients. The technical aspects of gene therapy administration for the treatment of hemophilia are relatively uniform with the capabilities of any reputable infusion center. However, there was strong agreement across all of the stakeholders that the specific considerations that lead to the initial treatment decision to administer gene therapy for hemophilia and for addressing complications after administration—such as liver enzyme elevation and the need for immune suppression—require the expertise and oversight of an HTC.

> "We've gone on record saying we believe it's in the best interest of patients to have gene therapy administered at HTCs."
>
> - NBDF Representative

> "My concern isn't about the actual administration of it. It's more the follow-up in the monitoring for potential toxicities and how they're managed with immune suppression."
>
> - HTC Physician

One specific issue surrounding HTC involvement in gene therapy administration is the variable resources and capabilities of the >140 centers across the United States. While larger, institution-based centers may have participated in gene therapy clinical trials and may be equipped to administer commercially available products, stakeholders voiced concern that smaller HTCs are likely not as well equipped. A solution to this may come from looking to the hub and spoke model deployed in Europe, where smaller centers (i.e., "the spokes") refer patients to a larger, centralized HTC (i.e., "the hub") for gene therapy administration.[8] The smaller centers are then responsible for following the patient and providing regular, ongoing care as they would under usual circumstances. In the United States, a similar strategy has been proposed and has garnered support from leaders in the bleeding disorders community. Stakeholders also noted that the regional HTC network in the United States lends itself to implementing such a model, although differences exist in the interconnectivity and geography among regions. Despite this potential and given the limited uptake of gene therapy thus far, no tangible steps have been taken toward implementing a hub and spoke model or any other approach for administration and follow-up across the regional HTC network.

> "Because uptake of gene therapy has been so limited thus far, I don't know that we've really had a chance to flesh out all the details of administration and follow-up."
> - HTC Physician

Access and Coverage Considerations

While the cost of gene therapy is greater than that of previous treatments, early evidence points to a substantially extended clinical benefit.[2,3,9] After a single gene therapy treatment, patients can produce their own clotting factor, negating the need for conventional treatment. According to data from clinical trials, the first approved hemophilia B gene therapy product has the potential to save 250,000 IU of factor IX concentrate per participant per year depending on disease severity and treatment regimen.[8] Having shown stable expression of factor IX level out to three years, the durability of the treatment effect is likely to be maintained for at least several years.[2,10] In addition, gene therapy has the potential to provide improved bleeding protection and quality of life than traditional prophylaxis with factor concentrates.[2,3] The higher cost of gene therapy should be considered in the context of the avoidance of continued factor replacement therapy and other components of health care resource utilization given sustained efficacy. Still, the prospect of a larger, potentially one-time drug acquisition cost presents a challenge for payers and the standard models used to cover and pay for prescription drugs.

> "I used to wonder when payers were going to ask HTCs to start taking risk on these patients because they are attached to such high costs. And we've always been able to push back and say, 'There's too much variability in this.' But now manufacturers are guaranteeing their products."
> - Hemophilia Alliance Representative

To overcome these challenges, gene therapy manufacturers and payers have turned to outcomes-based contracting to share the financial risk.[10,11] Manufacturers have announced intentions of reimbursing up to 100% of the cost of gene therapy should patients fail to respond or cease to respond in the first four years after administration.[11] Similar arrangements have been made in Europe, where the timeline for commercial availability of hemophilia gene therapy is slightly ahead of that of the United States.[12] Still, a growing majority of US payers have coverage policies in place for hemophilia gene therapy, and the importance of an outcomes-based contract is being conveyed to self-funded and fully insured employers as well.

The stakeholders identified barriers to optimal coverage and access among payers, which include exclusive specialty pharmacy contracts and narrow networks that exclude HTC involvement. Although specialty pharmacies are being leveraged for their purchasing power to supply products, stakeholders reiterated that HTCs should have a central role in gene therapy administration and—most importantly—follow-up. Echoing the recommendations of NBDF and the Hemophilia Alliance, the Institute for Clinical and Economic Research (ICER) has published that payers should require the delivery of gene therapy for hemophilia to be performed by or in consultation with an HTC.[13]

The Value of Multistakeholder Education

First-generation gene therapy for hemophilia does not qualify as a cure, although it has the potential to substantially mitigate disease and treatment burden across several years for a specific group of patients. Furthermore, gene therapy cannot completely supplant current factor replacement therapy or non-factor therapy, and additional novel treatment options will likely enter the space soon. In this manner, first-generation gene therapy along with a cache of other treatment options offers the potential to fulfill the unmet needs of a greater number of patients now more than ever before.

> "In the bleeding disorders community, there needs to be a lot of discussion surrounding what gene therapy follow-up looks like, what it means in their daily living, and what its impact is on their daily living. Steroid treatment is something they might not have experienced before."
>
> - Hemophilia Alliance Representative

While hematologists and other experts in the field are often well-versed in the nuances of gene therapy for hemophilia, patients must also be extensively informed to make sound decisions regarding their own treatment. Ultimately, clinically appropriate prescribing and evidence-based coverage and access are vital for optimal utilization of gene therapy and other emerging therapies, which requires multistakeholder education among providers and payers in addition to patients. Only HTCs—serving as the original medical home for patients with bleeding disorders—can provide the expert, interdisciplinary care, and ongoing 24/7 support necessary to optimize gene therapy administration and follow-up. Furthermore, the HTC care team is best equipped to educate patients on the various clinical considerations surrounding gene therapy as well as counsel them on personal aspects such as impact on daily living, coverage and access issues, and affordability in general. By informing the bleeding disorders community and practicing a shared decision-making process through the HTC, payers and manufacturers can rest assured the most ideal candidates for gene therapy have been effectively identified, offering favorable outcomes for all vested stakeholders.

Collaborative Opportunities Through CCSC

CCSC remains committed to serving the bleeding disorders community by facilitating the sustainability of the HTC-integrated comprehensive care model and promoting high-quality, cost-effective care, regardless of the specific treatment modality involved. As utilization of gene therapy progresses and additional treatments are approved, CCSC will continue to play a role in educating the payer community and fostering collaboration between health care providers, payers, and purchasers.

> "From a consumer perspective, we're really focused on the shared decision-making process — ensuring that both providers and patients can determine whether gene therapy is the right move together."
>
> - NBDF Representative

To find out more about how your organization can get involved, please visit **CCSC*Hemo*.com**.

References

1 Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, Fukazawa N, Yoneyama K, Yoshida H, Nogami K. Factor VIII-Mimetic Function of Humanized Bispecific Antibody in Hemophilia A. *N Engl J Med*. 2016;374(21):2044-53.

2 Mahlangu J, Kaczmarek R, von Drygalski A, Shapiro S, Chou SC, Ozelo MC, Kenet G, Peyvandi F, Wang M, Madan B, Key NS, Laffan M, Dunn AL, Mason J, Quon DV, Symington E, Leavitt AD, Oldenburg J, Chambost H, Reding MT, Jayaram K, Yu H, Mahajan R, Chavele KM, Reddy DB, Henshaw J, Robinson TM, Wong WY, Pipe SW; GENEr8-1 Trial Group. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. *N Engl J Med*. 2023;388(8):694-705.

3 Pipe SW, Leebeek FWG, Recht M, Key NS, Castaman G, Miesbach W, Lattimore S, Peerlinck K, Van der Valk P, Coppens M, Kampmann P, Meijer K, O'Connell N, Pasi KJ, Hart DP, Kazmi R, Astermark J, Hermans CRJR, Klamroth R, Lemons R, Visweshwar N, von Drygalski A, Young G, Crary SE, Escobar M, Gomez E, Kruse-Jarres R, Quon DV, Symington E, Wang M, Wheeler AP, Gut R, Liu YP, Dolmetsch RE, Cooper DL, Li Y, Goldstein B, Monahan PE. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. *N Engl J Med*. 2023;388(8):706-718.

4 US Food and Drug Administration. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/beqvez.

5 CSL Behring Announces the First Patient Has Received FDA-Approved HEMGENIX® (etranacogene dezaparvovec-drlb) for Hemophilia B. [Press Release]. CSL Behring. Published June 20, 2023. Accessed April 2024. https://www.prnewswire.com/news-releases/csl-behring-announces-the-first-patient-has-received-fda-approved-hemgenix-etranacogene-dezaparvovec-drlb-for-hemophilia-b-301854676.html

6 van Overbeeke E, Michelsen S, Hauber B, Peerlinck K, Hermans C, Lambert C, Goldman M, Simoens S, Huys I. Patient perspectives regarding gene therapy in haemophilia: Interviews from the PAVING study. *Haemophilia*. 2021;27(1):129-136.

7 Witkop M, Morgan G, O'Hara J, Recht M, Buckner TW, Nugent D, Curtis R, O'Mahony B, Skinner MW, Mulhern B, Cawson M, Ali TM, Sawyer EK, Li N. Patient preferences and priorities for haemophilia gene therapy in the US: A discrete choice experiment. *Haemophilia*. 2021;27(5):769-782.

8 Miesbach W, Chowdary P, Coppens M, Hart DP, Jimenez-Yuste V, Klamroth R, Makris M, Noone D, Peyvandi F. Delivery of AAV-based gene therapy through haemophilia centres-A need for re-evaluation of infrastructure and comprehensive care: A Joint publication of EAHAD and EHC. *Haemophilia*. 2021;27(6):967-973.

9 Chou SC, Hsu YC, Lin SW. Gene therapy for hemophilia, a clinical viewpoint. *J Formos Med Assoc*. 2023;122(11):1101-1110.

10 Pipe S, van der Valk P, Verhamme P, et al. Long-Term Bleeding Protection, Sustained FIX Activity, Reduction of FIX Consumption and Safety of Hemophilia B Gene Therapy: Results from the HOPE-B Trial 3 Years after Administration of a Single Dose of Etranacogene Dezaparvovec in Adult Patients with Severe or Moderately Severe Hemophilia B. *Blood*. 2023;142(Suppl 1):1055.

11 Hagen T. Manufacturers Adopt 'No Cure, No Pay' Pricing for Hemophilia Gene Therapies. *Managed Healthcare Executive*. Published August 9, 2023. Accessed April 2024. https://www.managedhealthcareexecutive.com/view/manufacturers-adopt-no-cure-no-pay-pricing-for-hemophilia-gene-therapy

12 BioMarin Announces Agreement with German Health Insurance Fund on Reimbursement Amount for ROCTAVIAN® (valoctocogene roxaparvovec-rvox) for Severe Hemophilia A in Germany. [Press Release]. BioMarin. Published November 28, 2023. Accessed April 2024. https://www.prnewswire.com/news-releases/biomarin-announces-agreement-with-german-health-insurance-fund-on-reimbursement-amount-for-roctavian-valoctocogene-roxaparvovec-rvox-for-severe-hemophilia-a-in-germany-301999249.html

13 Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Final Policy Recommendations. Institute for Clinical and Economic Research. Published December 22, 2022. Accessed April 2024. https://icer.org/wp-content/uploads/2022/12/ICER-Hemophilia-Policy-Recommendations-122222.pdf

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