Gene Therapies Pave the Way to a Potential Cure for Sickle Cell Disease

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Gene therapy is at a pivotal juncture of scientific promise and clinical transformation. One of the most underserved disease populations in which gene therapy shows promise is that of sickle cell disease (SCD). In the midst of tremendous clinical accomplishments, it is incumbent upon stakeholders to coordinate efforts to broaden the availability of gene therapies to patients with SCD and help bring therapeutic approaches closer to a cure. The burden of illness, technological advancements, evidence generation strategies, and reimbursement approaches involved each warrant consideration to inform a range of adaptive commercialization strategies in the successive analyses.

Sickle Cell Disease Presents a High Unmet Need for Disease-Modifying Therapies

SCD is the most common inherited hemoglobin disorder, affecting an estimated 100,000 individuals in the United States (US) and millions of people worldwide.[1] It is the first disorder for which a molecular cause was identified: a single mutation in the β-globin gene causing the polymerization of hemoglobin S. The resulting distorted, crescent-shaped cells stick to blood vessels, damaging their endothelia and ultimately causing blockages that lead to sluggish or obstructed blood and oxygen flow.[2]

Patients with SCD suffer from episodes of acute pain caused by vaso-occlusive crises (VOCs), including acute chest syndrome, leading to irreversible end-organ damage, poor quality of life, and stroke.[3,4] The consequences and costs of such complications are overwhelming at both humanistic and economic levels, including the reduction of lifespans of individuals with SCD, and result in an estimated annual cost of hospitalization due to SCD-related complications of $488 million in the US alone.[4,5] Similarly, the total cost of medical care for children and adults in the US with SCD has been estimated at over $1.1 billion, presenting an additional frame of reference for the potential cost offset of curing this disease.[6]

Although the genetic basis of SCD was discovered nearly 70 years ago, potentially curative therapies targeting the β-globin gene mutation are not yet widely available.[7] Allogeneic hematopoietic stem cell transplantation is currently the only curative option for SCD, but limited availability of suitable donors and the high risk of transplant-associated complications are obstacles to its widespread use.[2,3] The development of disease-modifying treatments (DMTs) is especially important because such treatments are not widely available; until the approval of L-glutamine in 2017, the established standard of care was hydroxyurea, which was approved over 20 years ago. Both agents have limited patient usefulness and many safety issues, similar to chronic blood transfusions.[4] Two agents were approved for SCD in 2019, crizanlizumab and voxelotor, though the former simply reduces VOC frequency and the latter lacks long-term safety data.[8–10] Ultimately, there remains an urgent unmet need to provide access to a cure for SCD.[11]

Multi-Stakeholder Commitment and Funding Have Been Devoted to Finding a Definitive Cure

The multidisciplinary SCD stakeholder community has rallied to expand access to the transformative therapies that are currently building clinical momentum. In 2016, the American Society of Hematology began the Sickle Cell Disease Coalition, and in 2018, the National Institutes of Health launched the National Heart, Lung, and Blood Institute Cure Sickle Cell Initiative to accelerate the development of therapies to cure SCD.[12] Calls for curative SCD technologies are growing stronger as patients, advocates, and legislators are voicing their demands for market access to curative SCD therapies.[13] Although progress is being made, many barriers to quality care in the US remain for SCD patients, including restricted access to health insurance, inconsistent provider experience and knowledge, lack of effective treatment options, and limited participation in clinical trials.[14]

One prominent approach to curative treatment is gene therapy, which involves collecting hematopoietic stem cells (HSCs) from a patient, followed by gene manipulation and reinfusion of genetically altered cells into the patient.[11] This therapy can yield a lifelong autograft that produces modified red blood cells and has the potential to revolutionize the treatment of SCD by providing a cure.[7,15] Gene therapy approaches currently under investigation include gene addition, gene editing, fetal hemoglobin (HbF) induction, and hybrid strategies.[2,4,7]

As shown in **Table 1**, investigational gene therapies in SCD that use the gene addition approach include Zynteglo™ (formerly known as LentiGlobin™), which contains a vector that encodes an anti-sickling β-globin variant.[16] An ongoing phase 1/2 study (HGB-206, NCT02140554) has provided inspiring glimpses of milestone progress, with a median of less than 50% of mutant hemoglobin reported among treated patients with at least 6 months of follow-up.[17] While Zynteglo is investigational for SCD, conditional European approval for β-thalassemia was granted in June 2019, while its commercial launch for that indication after meeting manufacturing requirements is not anticipated to occur until early 2020.[18] Another gene addition approach utilizes RVT-1801 (NCT02186418), which contains a lentiviral vector with the gamma-globin gene for the production of HbF.[19]

Investigational gene therapies in SCD that use gene editing include CTX001 and BIVV003, which contain autologous CD34+ HSCs. These approaches leverage CRISPR/Cas9 and zinc finger nuclease (ZFN) gene-editing technologies, respectively, that can facilitate disease modification by increasing HbF production through silencing an HbF repressor such as *BCL11A*. Both CTX001 and BIVV003 are in phase 1/2 studies in patients with severe SCD and are currently recruiting participants (NCT03745287, NCT03653247). The investigational products described are each administered intravenously, followed by a one-time post-conditioning regimen.

Table 1. Autologous HSCT Gene Therapies

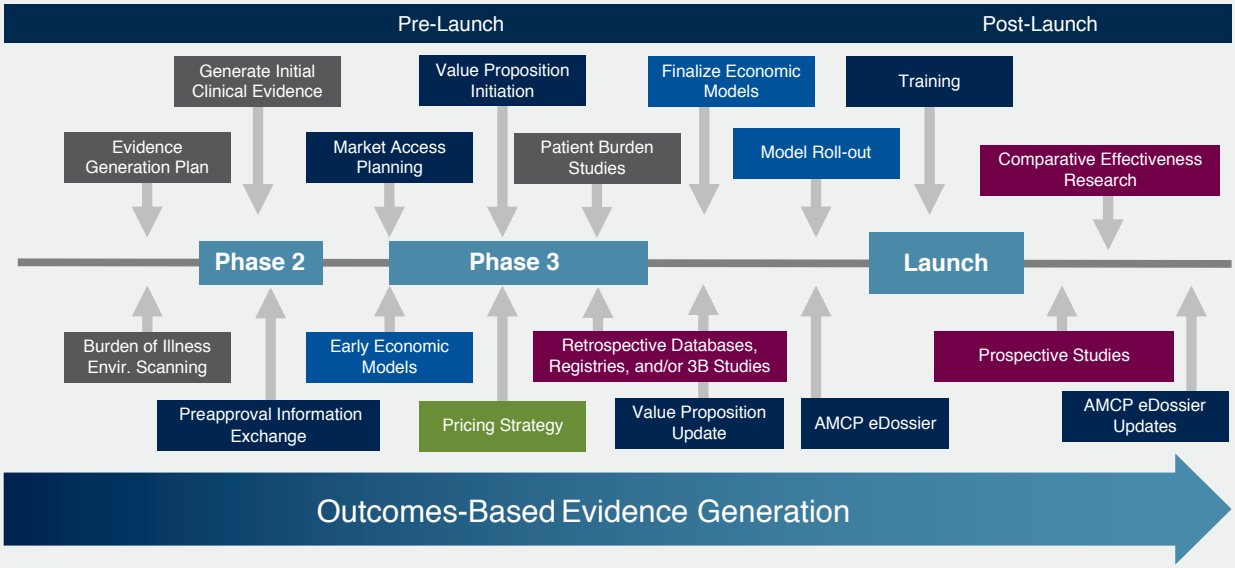
Drug	Targets	Vector or Technology	Designation	Study
Zynteglo (LentiGlobin)	Hemoglobin	BB305 lentiviral vector	Fast Track and RMAT	Phase 1/2, N=50 estimated NCT02140554
RVT-1801		Gamma-globin lentiviral vector	N/A	Phase 1/2, N=10 estimated NCT02186418
CTX001	*BCL11A*	CRISPR/Cas9	Fast Track	Phase 1/2, N=45 estimated NCT03745287
BIVV003		ZFN mRNA	N/A	Phase 1/2, N=8 estimated NCT03653247

Key: CRISPR/Cas9 – clustered regularly interspaced short palindromic repeats-associated protein 9; HSCT – hematopoietic stem cell transplant; mRNA – messenger ribonucleic acid; N/A – not applicable; RMAT – regenerative medicine advanced therapy; ZFN – zinc finger nuclease.

Successful Commercialization of Gene Therapies in SCD Needs to Focus on Timely Access and Reimbursement

Gene therapies have the potential to address longstanding unmet clinical needs in SCD by providing a curative treatment to patients suffering from debilitating symptoms and life expectancy that is shortened by an estimated 22 years.[20] Despite auspicious early clinical results, the high short-term costs due to a 1-time treatment may present access barriers to these innovative therapies, but they are likely to be less expensive than 30 to 40 years of the disease's chronic, long-term complications that often result in premature death. Nevertheless, such value arguments rely on long-term efficacy measures that cannot be collected prior to commercial launch and reimbursement arrangements, leaving treatment accessibility an open question. Also, such therapies present complex logistical challenges that require proactive management to ensure patient safety and access to care. Commercialization strategies may be affected by a variety of factors unique to gene therapies in SCD, including patient-specific therapeutic preparation, lengthy manufacturing requirements, small patient populations, geographic distribution, and lack of long-term efficacy and safety data. For these reasons, traditional market access strategies need to be modified to overcome the challenges associated with these novel products and maximize opportunities for successful commercialization, as illustrated in Figure 1.[14,21]

Figure 1. Timing of Evidence Development Considerations for Gene Therapy Manufacturers



Color key: grey: health economics and outcomes research; blue: modeling; navy: value messaging; red: database studies; green: pricing.
Note: Other activities may be included depending on the product or market scenarios.

Key: AMCP – Academy of Managed Care Pharmacy; HEOR – health economics outcomes research.

Expanding Patient Access Requires Developing Comprehensive Solutions

Although the transformative potential of gene therapies has garnered considerable enthusiasm, their limited number and treatable populations have not substantially tested existing reimbursement models, which are designed to address primarily acute illnesses with incremental interventions. Recent market developments have illustrated the expectation of approvals for new gene therapeutics, which will expand the treatable patient populations beyond the working capacity of standard reimbursement models.[22] The 7 cell and gene therapies in clinical trials for SCD present a strong likelihood that one of these therapies will be approved, with commercial launches anticipated to occur as early as 2020, all but guaranteeing a paradigm shift within SCD therapy.[23]

Importantly, payers have expressed optimism that demonstrating the value of transformative therapies will be more attainable in diseases with greater unmet medical needs like SCD.[24] However, providers and payers must receive practical guidance in reimbursement methodologies in order to facilitate patient access to treatment.[25,26] Likewise, providing equitable access, especially among aging and pediatric populations, requires Medicare and Medicaid reimbursement policies that address the possibility of hospitals facing losses for direct costs unaddressed by bundled Medicare payments.[26] Importantly, investigational sites and Prospective Payment System-exempt hospitals would be best positioned to facilitate access, since such facilities are able to administer gene therapy and are offered a financial incentive to do so via exclusion from payment bundling.[27]

Other archetypes being evaluated for transformative therapies include payment models like revenue caps and milestone payments, as well as financing models such as patient assistance or subsidies, re-insurance, supplier credits, and consumer mortgages or annuities, each with intrinsic risks and benefits for providers, payers, manufacturers, and patients.[25] Novel suggestions to defray patient costs include manufacturers paying for any added conventional therapies needed by the patient.[22] Amidst such a plethora of potential models, market access success can only arise via strategic payment models that facilitate adoption in the target populations.[25] Furthermore, a comprehensive reimbursement coding strategy that includes early evaluation and provider education is crucial to the commercial viability of such innovative therapies.[28]

Patients themselves certainly struggle with a number of aspects of gene therapies. Optimism about curative gene therapies is tempered by a limited understanding of the paradigm shift offered by these treatments—and the daunting upfront costs of approved therapies, with estimates ranging from $373,000 to $2,100,000.[25,26,29,30] The approval of Zynteglo for β-thalassemia gives an even more challenging economic prospect for subsequent approval in SCD, since its price has been set at $1.8 million over 5 years.[31] Appreciating these challenges, manufacturers of approved gene therapies already offer patient support programs to negotiate logistics and payments, including insurance, travel, and accommodations throughout treatment.[26] Nevertheless, the current price of gene therapies steeply discourages patients in general, and particularly those of limited means whose only access may come from navigating the complexities of government health programs such as Medicare and Medicaid.

One formidable hurdle for Medicaid reimbursement is a law known as Medicaid Best Price, which, among other provisions, requires manufacturers to offer a 23% discount or the lowest negotiated price for Medicaid patients. Such considerations have watershed implications for value-based contracting as tantamount to discounting therapies that are unable to meet outcomes goals for the entire Medicaid patient population.[22] Similar challenges are expected to arise from the considerable slant toward Medicaid coverage among SCD patients, which could generate a sizable tax burden from Medicaid charges and force manufacturers to increase prices on non-Medicaid patients to counterbalance the utilization of discounts.[32]

Market Access Will Arise From Collaborations With a Range of Stakeholders

The high costs of gene therapies are counterbalanced by their economic value in alleviating subsequent healthcare burdens, but calculating these values and ensuring patient access for expensive therapies remain considerable yet illuminating challenges. For example, estimates of the escalating cost of care for an average patient with SCD approach $1 million by age 45, largely arising from sequelae and symptom (especially pain) management in the absence of broadly applicable DMTs.[6] Nevertheless, providing patient access is an active focus for payers, whose success in doing so depends on interactions with manufacturers and regulators alike. Policy makers rely on balancing short-term affordability with long-term value, wherein considerable complexity arises in calculating direct and indirect costs. Moreover, the methodologies for such regulatory calculations are undergoing active reevaluation.

It is particularly important that gene therapy manufacturers leverage preapproval information exchange (PIE) to engage early and often with payers via cooperative partnerships, including a broad variety of engagements that shape validated patient access strategies. The acceptance of gene therapies among commercial payers has likewise influenced policies issued by the Centers for Medicare & Medicaid Services, whose recent policy considerations include placing chimeric antigen receptor T-cell (CAR-T) therapy in a higher-weighted diagnosis-related group and approving manufacturer applications for New Technology Add-on Payments to reimburse Medicare patients.[26] Among the potential solutions being evaluated in the marketplace are specialty pharmacy installment plan arrangements with payers and manufacturers. Payers, manufacturers, and regulators have voiced joint support for outcomes-based contracts (with rebates and installment payments), as well as for contract input from providers, payers, and manufacturers.[25,26] Likewise, independent organizations such as the Institute for Clinical and Economic Review have yielded evolving standards for health technology assessments that are reshaping value conversations, including expanded cost-effectiveness ratio thresholds of up to $175,000 per quality-adjusted life-year (QALY).[29]

Gene Therapy Coverage Requires Specialized Contracting and Real-World Evidence

Payers have shown notable enthusiasm about outcomes-based contracts for gene therapies for their potential to ensure that only superior outcomes are reimbursed at the high costs set by their manufacturers.[32] Therefore, commercial viability may increasingly depend on leveraging the limited clinical data available at commercial launch into favorable contracting terms. Companies in this commercial space may be able to capitalize on patient data, such as that from Medicare, Medicaid, and patient registries.[26]

Stakeholders have struggled to establish essential parameters by which to calculate appropriate levels of cost and reimbursement. For example, popular calculation methods, such as QALYs, are often inappropriate for the small patient numbers and variable outcomes within clinical studies for gene therapies. Partly as a result, popular arrangements for flexible patient support, such as value-based contracting, have struggled within the gene therapy landscape. Moreover, stakeholders must contend with a range of practical challenges when evaluating reimbursement models for gene therapies, including limiting the burden of upfront costs, the scalability of existing payment models, and policy and legislative hurdles. Insurers prefer distributing reimbursements over time, but calculating and negotiating the balance of reimbursements is complicated by "beneficiary churn," in which patients change insurers over the course of their putatively improved outcomes.[33,34]

Real-world evidence must be gathered and examined carefully in order to evaluate the most appropriate approaches to defray upfront costs for breakthrough technologies. Such evidence may be utilized in outcomes-based contracts to limit payer exposure, which are already being offered for the approved gene therapy Luxturna® (voretigene neparvovec-rzyl). Additionally, installment reimbursement and contracting with commercial payers or specialty pharmacies are being utilized to encourage treatment center adoption. Though cumbersome, outcomes-based contracting has been implemented for the CAR-T therapy Kymriah™ (tisagenlecleucel).[26]

With the many challenges associated with these therapies, manufacturers must look at unique solutions and collaborate with stakeholders in creative ways to increase their chances of achieving market access success (**Table 2**).

Table 2. Avenues for Manufacturer Collaborations

Key Considerations for Manufacturers	Solutions
 Develop therapy-specific patient support systems	▪ Innovative payment models ▪ Specialized reimbursement field teams ▪ Proactive clinician and provider education
 Collaborate with many types of stakeholders	▪ Advisory boards ▪ Strategic market intelligence (payer/provider/patient insights) ▪ Early value proposition development
 Generate real-world evidence	▪ Illustrative data (epidemiology, burden of disease, treatment patterns) ▪ Scientific slide decks, posters, and manuscripts ▪ Economic models (budget impact) ▪ Long-term outcomes via prospective/retrospective studies

Conclusions

Gene therapies offer unparalleled promise for alleviating the humanistic and societal burdens imposed by SCD. At the same time, such innovative therapies pose unprecedented challenges in their economic costs across diverse patient populations. The strong likelihood of approval of at least one such therapeutic is poised to challenge the reimbursement landscape in SCD, which will require market expertise to navigate effectively. It is incumbent upon gene therapy manufacturers to seize opportunities to engage stakeholders in building patient support systems, exploring innovative payment models, leveraging powerful relationships with a variety of stakeholders, and developing bodies of real-world evidence. Amidst considerable market access challenges, manufacturers need to rethink their traditional go-to-market models by partnering with organizations such as Xcenda, LLC (www.xcenda.com), who have supported the successful launch of gene therapies marketed in the US. By doing so, gene therapies may deliver on their potential to reach and treat patients in a transformative way.

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