High-Priced Sickle Cell Gene Therapies Threaten to Exacerbate US Health Disparities and Establish New Pricing Precedents for Molecular Medicine

Health Policy Portal

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Abstract: Gene therapies to treat sickle cell disease are in development and are expected to have high costs. The large eligible population size — by far, the largest for a gene therapy — poses daunting budget challenges and threatens to exacerbate health disparities for Black patients, who make up the vast majority of American sickle cell patients.

Important medical advances are emerging for the treatment of sickle cell disease (SCD). In November 2019, the US Food and Drug Administration (FDA) approved crizanlizumab-tmca (Adakveo), a once-monthly medication proven to reduce the number of sickle cell pain crises, and voxelotor (Oxbryta), which inhibits the sickling and destruction of red blood cells, improving hemoglobin levels for patients.[1] Allogeneic bone and marrow transplantation has also emerged as a promising SCD therapy but is limited by the availability of matched related donors. Other transformative treatments are on the horizon. Several companies are developing gene therapies that would insert a functional copy of the beta-globin gene into the blood-producing hematopoietic stem cells of patients with SCD using viral vectors and gene editors like CRISPR.[2] These alterations have the potential to prevent erythropoietic sickling and to eliminate pain crises and their sequelae.[3]

Although the science and therapeutic benefit of such treatments are promising, the economic realities of paying for such drugs are troubling. In the US, crizanlizumab-tmca and voxelotor cost about $100,000 per year, and the price of sickle cell gene therapies may far surpass this at an expected cost of over $1 million for one-time treatment.[4] Similar prices are expected for gene therapies to treat hemophilia and beta-thalassemia. In Europe, a beta-thalassemia gene therapy, betibeglogene autotemcel (Zynteglo), already sells for $1.8 million.[5]

Such prices have been justified on the basis of long-term savings to the health care system from reduced disease management costs.[6] However, payment models for gene therapies may not be scalable for commonly occurring ailments like SCD. For example, the roughly 100,000 US patients with SCD is far larger than any other eligible populations for FDA-approved gene therapies.[7]

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About This Column

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Although the patient population is very large by gene therapy standards, it would qualify SCD therapies for special status under the US Orphan Drug Act, which may explain, in part, their high prices. Recently, rare disease drug prices have been rising.[8] However, even for a rare disease drug, the price of SCD therapies at $1 million or more would be astronomically high: the average annual cost for rare disease drugs was $138,919 from 2008 to 2017.[9]

Payers have struggled with the budget impact of expensive drugs for both small numbers of patients, even when these drugs are extremely effective.[10] After the 2013 approval of sofosbuvir (Sovaldi) — a curative treatment for hepatitis C virus infection that was initially priced at $84,000 for a course of treatment — many states restricted its access to otherwise eligible Medicaid patients and those in the prison population.[11] Private payers also struggled to afford sofosbuvir.[12] Moderate price reductions from competition due to comparable products made by other manufacturers have since allowed greater access to products treating hepatitis C virus, but public insurers are still spending substantial sums on these drugs. The number of patients with SCD combined with the expected drug prices will have a similarly significant budget impact for payers, which will, in turn, likely restrict drug access to patients.

The cost of SCD therapies will likely be a major barrier in accessing care, and may, because of the demographics of SCD patients in the US, also exacerbate existing racial health disparities experienced by Black Americans. The vast majority of US patients with SCD are Black — an estimated 1 in 365 Black Americans have the disease as compared to roughly 1 in 93,000 White Americans.[13] Additionally, 1 in 13 Black Americans are carriers of sickle cell trait — a milder, related condition that increases risk of chronic kidney disease and venous thromboembolism — and may one day also be treated with gene therapies.[14]

US gene therapy prices have recently reached from $475,000 to over $2 million for one-time use.[15] But the case of SCD therapies brings an additional consideration into the drug pricing ecosystem: how should health equity be incorporated into pricing? Should manufacturers have the unilateral power to set an unfettered price for a treatment benefiting a population with historical health disparities whose medical needs have been long under-researched and under-funded? The emergence of high-priced SCD treatments also raises the question of how the US federal government's contribution to SCD gene therapy development should impact its price.

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Price-Setting Considerations for Expensive Sickle Cell Disease Treatments

The classic justification for drugmakers being able to set their own prices in the US has been the high cost of research and development, but pharmaceutical manufacturers — influenced by existing market incentives — have long under-invested in SCD research and development. Indeed, over the past two decades, SCD has been under-researched and under-funded compared to other diseases with similar or lower incidence in the US, even though the average life expectancy of people with the disease is just 54 years.[16] Compounding this problem, historical under-investment is often used to justify higher prices. Since a drug treats a population with a health disparity, the argument goes, manufacturers should be better rewarded for developing a drug to treat the population. But why should systematic biases against certain populations be later weaponized to cost those patients more?

While the private market has not provided much funding for SCD research, the US government does appear to have played a substantial role in funding SCD gene therapy development via the National Institutes of Health (NIH). Viral vector technology, designed for use in SCD gene therapy, was developed, in part, at the NIH through its intramural research program.[17] In 2019, the NIH announced plans to invest an additional $100 million into the development of SCD gene therapies.[18] CRISPR technology, a therapeutic treatment modality for SCD therapy, was developed at academic institutions with extensive NIH support.[19]

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Also, ongoing clinical trials to study the effects of SCD gene therapies received funding from the NIH, with some studies using NIH facilities in Bethesda, Maryland as a trial site.[20]

Manufacturers producing the gene therapy may contend that a $1 million or more price tag is justified because treatment at such a price offers value to the health care system, which would be expected to pay slightly more than this amount in costs to treat a SCD patient over a lifetime. But this reasoning is concerning in several ways. First, since even a fraction of this price would be difficult for nearly any American to pay out-of-pocket, access to the drug would be limited to patients with insurance. However, it has historically been the case that Black Americans have had lower rates of health insurance and underinsurance of coverage as compared to non-Hispanic White Americans across all age groups, increasing the risk of exposure to high out-of-pocket costs.[21] As such, it would be difficult to achieve "pharmacoequity" — fair access to prescription drugs regardless of race or socioeconomic background — an issue bearing special attention in the wake of protests to bring greater racial equity to the US health care system.[22]

For SCD patients with health insurance, coverage decisions — especially by government insurers — may also lead to unethical outcomes. Medicaid is now the largest insurer of SCD patients — over 55,000 out of the roughly 100,000 SCD patients in the US were insured through the program in June 2019.[23] To pay for 55,000 sickle cell gene therapies at a price of $1 million per dose, Medicaid would have to pay $55 billion, over 85% of Medicaid's national spend for outpatient drugs in 2017. By contrast, the hepatitis C virus treatments sofosbuvir (Sovaldi) and ledipasvir/sofosbuvir (Harvoni) cost Medicaid about $2.8 billion in 2015.[24]

For individual state Medicaid programs, paying for SCD gene therapies would consume disproportionate percentages of their budgets. In the state of Illinois, for example, 2020 Medicaid spending allocated to "prescribed drugs" was $872 million.[25] There are an estimated 3,500 patients in Illinois with SCD.[26] If about 55% of these patients were on Medicaid — the average percentage nationally — and SCD gene therapy cost $1 million, then it would cost $1.925 billion, about 2.2 times the amount needed to cover *all* Medicaid outpatient drugs in a state with a population of over 12.5 million people. Even if only 875 out of the estimated 1,925 Medicaid-covered SCD patients in Illinois—about 45% of this population—received SCD gene therapy, the total spending on 875 patients would still exceed Illinois Medicaid spending for all outpatient drugs in the state. Thus, SCD gene therapy's expected price-point would severely challenge government budgets, potentially limiting Medicaid's ability to pay for its current drugs and services.

Alternative Pricing Options for Sickle Cell Disease Therapies

In light of the US federal government's contribution to SCD gene therapy development and the impending effect that its price may have in exacerbating health care disparities, there is a strong case that legislative bodies should prospectively address SCD gene therapy prices. In a June 2019 opinion piece, US Senator Bill Cassidy (R-LA) hinted at the possibility of bipartisan-supported payment strategies to make SCD gene therapies more affordable.[27] He suggested that payors could use a subscription model of payment, in which a lump sum was paid by each state's Medicaid office to cover all SCD patients — a strategy that was previously used by Louisiana to purchase hepatitis C virus treatments like sofosbuvir for its Medicaid patients.[28] Cassidy also suggested the creation of a payor collaboration for a curative gene therapy fund, into which Medicaid and private insurers would make contributions. This fund would be used to pay for all SCD gene therapies. Since payment for therapies would be carved out of premiums, all insurers and users of the gene treatment would get the same price.[29]

Cassidy additionally suggested that gene therapies could be priced in a prorated fashion that incorporates the cost of past treatment care and future life expectancy. For example, a 30-year-old sickle cell disease patient with a current life expectancy of 54 years might not pay $1 million for treatment, but rather $1 million divided by 54, about $18,500 per year for nearly a quarter of a century.[30] However, this payment strategy would have important problems. First, it would subject patients to crippling debt sustained over decades, which may exacerbate low socioeconomic conditions for Medicaid eligible patients. Additionally, issues of insurance coverage could further complicate the plan. What would happen if a patient changed insurance? In the installments plan, private insurers would likely have strong incentives to delay treatment in the hopes that patients would switch to another third-party payor.

Nevertheless, payment strategies that extend the length of payments may play a role in paying for SCD gene therapies. In devising such reforms, officials should not take as a starting point the price tag set by the manufacturer without the input of payers. The price of the therapy should be negotiated by government based on its clinical benefits as well as the government's support for the development of technology, patients' ability to afford the medication, and health equity concerns. For drug products like SCD gene therapies with significant development support from US federal funding, there have been previous calls to mandate reasonable pricing as a condition of transferring relevant intellectual property rights to manufacturers and calls to leverage federal support of drug development in price negotiations by federal payers.[31] This latter strategy might be applied by Medicaid and the Children's Health Insurance Program to bring to manufacturers' attention the NIH's federal support of SCD therapy development. Federal payers could thus avoid having the government "pay-twice" for drugs — once for development, again for purchase.

Another related policy proposal would be the enactment of a federal review board, charged with

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determining the equitability of pricing for products costing more than $500,000 for one-time use (perhaps in conjunction with existing organizations that evaluate the appropriateness of pharmaceutical pricing). Such a board could be encouraged not to use equity considerations as a way to increase the price of a drug (as a recent health technology assessment did),[32] but rather, as a way to offer greater social value — reducing the budget burden on state Medicaid offices, which could use millions of dollars in savings to reinvest in underserved communities. Such pricing would faithfully acknowledge the original intent of publicly funding sickle cell research — to improve disparities by designing new therapies, not exacerbate them by setting prices that gatekeep patients from these medicines.

Conclusion

In today's drug development system in which companies have sole authority to set price in the US market, important factors like equity and public funding contribution to drug development are unlikely to be factored into pricing. As SCD therapies are developed and brought to market, it will be critical to think of strategies that price sickle cell agents in ways that fairly reward manufacturers for any risky private investments they made in paradigm-shifting medications with federal support and also make medications available to those who stand to benefit from the treatment.

All solutions to this problem must begin with acknowledgement that in today's drug development system there are misaligned incentives that allow for the inequitable pricing and production of pharmaceuticals. In 2022, the pricing of drugs already exacerbates health and socioeconomic inequities, which are not factored into drug pricing policy decision-making. With the emergence of gene therapies, this trend will only become worse.

In a system in which drug companies have sole authority to set price, important factors like equity and public funding contribution to drug development will be unlikely to be factored into pricing. There needs to be a re-alignment of market incentives that encourages development of fairly-priced treatments for populations with historical health disparity to help patients who have been underserved by medicine in the past and should not be again.

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