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Perspective

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Cell and Gene Therapies — Improving Access and Outcomes for Medicare and Medicaid Beneficiaries

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An executive order issued by former president Joe Biden in October 2022 tasked the Department of Health and Human Services (HHS) with directing the Center for Medicare and Medicaid Innovation (CMMI) to develop and test payment and delivery models that would lower drug costs and promote access to innovative therapies for Medicare and Medicaid enrollees. In February 2023, HHS proposed three models that CMMI could consider (the future of the models is uncertain, given the change in administration). Two of the approaches have yet to be formally announced and seem likely to address payment policies — one model would reduce out-of-pocket costs for high-value generic drugs, and another would be aimed at hastening confirmatory-trial completion for drugs that have received accelerated approval from the Food and Drug Administration (FDA), most likely by adjusting Medicare payments for such drugs.

The third approach, the Cell and Gene Therapy Access Model, which was formally announced in August 2024,[1] goes beyond typical payment-policy frameworks. The model supports voluntary, outcomes-based agreements between state Medicaid programs and cell- and gene-therapy manufacturers. The first iteration will apply to gene therapies authorized by the FDA for treating sickle cell disease (SCD); the model will aim to align coverage and payment for expensive therapies with outcomes among Medicaid and Medicaid-expansion Children's Health Insurance Program (CHIP) beneficiaries.

The Centers for Medicare and Medicaid Services (CMS) and pharmaceutical manufacturers negotiated key terms — including prices, payment-agreement structures, eligibility, and outcome measures — that were finalized on December 4, 2024, and will form the basis for contracts between manufacturers and states participating in the model. Terms were disclosed to states, and state Medicaid agencies can apply through February 2025 to begin participating between January 2025 and January 2026. The details of the terms agreed to by CMS and manufacturers may set a precedent for future cell- and gene-therapy access models that apply to broader groups of Medicaid and Medicare beneficiaries.

The FDA classifies cellular immunotherapies, cancer vaccines, and other types of autologous and allogeneic cells used for therapeutic indications as cellular therapies. Products that modify or manipulate the expression of a gene or alter the biologic properties of

living cells are considered gene therapies. These treatments are provided in discrete episodes of care and address underlying disease causes, with the goal of providing durable improvements in outcomes for patients. As of December 2024, the FDA had approved 41 cell- or gene-therapy products, with prices ranging from $500,000 to more than $4 million. These prices don't include physician and facility costs associated with treatment administration. Two gene therapies are authorized by the FDA for treating SCD: exagamglogene autotemcel (exa-cel; Casgevy) and lovotibeglogene autotemcel (lovo-cel; Lyfgenia), both of which are approved for patients 12 years of age or older with a history of vaso-occlusive events. Prices for these therapies in the United States are $2.2 million and $3.1 million, respectively.

Exa-cel was authorized on the basis of results from one clinical trial, a single-group, open-label study involving 44 patients who were followed for an average of 19 months. Of the 30 patients who were followed for at least 12 consecutive months, 29 (97%) remained free from vaso-occlusive events and all 30 remained free from hospitalizations for vaso-occlusive events over that period.[2] Lovo-cel was also authorized on the basis of results from one clinical trial, an ongoing single-group, open-label study involving 54 patients who were followed for 24 months for the primary analysis. Of the 32 patients who met the criteria for evaluation, 28 (88%) had a complete resolution of vaso-occlusive events by 6 to 18 months after infusion.[3] Both trials enrolled only patients who had had at least two severe vaso-occlusive events each year for at least 2 years. Nearly all patients had at least one adverse event; more than half of patients had a serious adverse event, such as febrile neutropenia or thrombocytopenia, and a small number died or developed a hematologic cancer. The package insert for lovo-cel includes a black-box warning about hematologic cancer.

Under an outcomes-based payment agreement, CMS could negotiate a reduced price with a manufacturer — a figure that could vary with the number of patients treated under the model — and would pay that amount only if the treated patient had the agreed-upon outcome (or could receive a rebate if they didn't). Such agreements can take various forms.[4] An agreement could be structured as a single, delayed payment, such that after a specified period, CMS would pay the full price if the treatment had worked and nothing if it hadn't. Alternatively, payments could be amortized, such that at specified intervals, CMS would pay a portion of the full price if the treatment was working and would stop paying if it stopped working. Finally, an agreement could include an outcomes-based rebate, whereby CMS would pay the full negotiated price at the time of treatment and the manufacturer would provide a partial or full refund or a "credit" to be used toward future treatment purchases if the treatment didn't work.

On the basis of the information available, it seems likely that agreements covering Medicaid beneficiaries will differ from those covering CHIP beneficiaries. In addition to questions about the final negotiated prices, there are important questions about how CMS and manufacturers structured the agreements. Will payments to manufacturers be delayed for 1 year (for example) after treatment, be amortized over a longer period, or rely on outcomes-based rebates? Since rebates are likely to be part of the agreements, there will probably be additional questions about terms (i.e., Will rebates cover the full cost of the therapy, or a percentage of it?), timing (i.e., Will rebates be provided after 1 year, or after a longer period?), and mechanisms for providing them (i.e., Will payments be returned by the manufacturer to CMS, or will future purchases be discounted?).

Questions remain about other issues as well. For instance, which beneficiaries with SCD will be eligible for treatment, and will eligibility depend on disease severity? What outcome measure (or measures) will be used for the agreements? Since both clinical studies were focused on resolution of vaso-occlusive events, it seems likely that agreements will use these events as an outcome measure. But will outcomes-based agreements define resolution on the basis of the absence of hospitalizations for vaso-occlusive events, office visits for these events, or disease-management interventions, such as red-cell transfusions or short-term opioid treatment? Additional measures could also be used, such as surrogate markers for antisickling-hemoglobin levels or patient-reported outcome measures, including symptom burden, quality of life, and functioning. Finally, will outcomes-based agreements also account for safety?

In many ways, SCD therapies were an ideal selection for the first iteration of this model. First, because SCD disproportionately affects Black (and, to a lesser extent, Latinx) people in the United States, the model addresses treat-

ments that are needed by patient groups that have historically experienced inequities and would be prohibitively expensive for many people. Second, more than half of people with SCD in the United States are enrolled in Medicaid or CHIP; many people with severe disease remain eligible for Medicaid into adulthood because of disability. Although these therapies require large, upfront payments, they appear to be generally effective within 1 year, which could help mitigate concerns about coverage shifts and Medicaid programs not benefiting from savings linked to reductions in disease exacerbations and complications over patients' lifetimes, as well as concerns about rebate terms, timing, and mechanisms. Third, vaso-occlusive events can be reliably identified using Medicaid claims data, since they typically result in hospitalizations or office visits. Using these events as the outcome measure in an outcomes-based agreement wouldn't require additional data-collection efforts to track patients across various health systems or to assess biomarker levels or patient-reported outcomes.

An audio interview with Joseph Ross is available at NEJM.org

Future agreements pertaining to cell- and gene-therapy access models may not be as straightforward, however, which could lead to concerns about the limited opportunity for public input and other precedents set by CMS in negotiations with the manufacturers of exa-cel and lovo-cel. Details related to prices, payment-agreement structures, beneficiary eligibility, and outcome measures are being disclosed to states, but they haven't been publicly released. Such terms may not be appropriate for therapies that are approved on the basis of less convincing evidence[5] or are less effective than SCD treatments, or for therapies whose effectiveness and safety are more difficult to monitor. Developing and testing payment and delivery models that could lower drug costs and promote access to innovative therapies is a smart policy decision. But getting the details right is critical to ensuring the success not only of the current model, but also of future cell- and gene-therapy access models for Medicare and Medicaid beneficiaries.

Disclosure forms provided by the author are available at NEJM.org.

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Pulling Out the Rug on Informed Consent — New Legal Threats to Clinicians and Patients

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In recent years, state legislators in large portions of the United States have devised and enacted new legal strategies to limit access to health care for transgender people.[1] To date, 26 states have enacted outright bans on gender-affirming care, which thus far apply only to minors. Other state laws create financial or procedural obstacles to this type of care, such as bans on insurance coverage, requirements to obtain opinions from multiple clinicians, or consent protocols that are stricter than those for other health care.[1]

These laws target clinicians who provide gender-affirming care, but all clinicians — in every jurisdiction and specialty — should take note of the intrusive legal actions that are emerging in the regulation of health care for transgender people. Like the development of restrictive abortion laws, new legal tactics for attacking gender-affirming care are likely to guide legislative opposition to other politically contested medical interventions. Here we consider one particular legal strategy that, if more widely adopted, could challenge the legal infrastructure underlying U.S. health care.

One new legal technique that restricts gender-affirming care for minors aims at a core component of the clinician–patient relationship: clinicians' responsibility to obtain patients' informed consent