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James X. Zhang & Lisa R. Shugarman

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EDITORIAL

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Introduction

Cell and gene therapies (CGTs) treat patients in ways different from traditional medical and surgical approaches by providing "living drugs" that can heal and replace damaged tissues or diseased organs[1]. These technological breakthroughs offer hope for curing many rare and hard-to-treat conditions, including blood disorders, cancer, eye disease, neurological disorders, and immune conditions[2]. However, due to the high cost of treatment, a relatively small pool of patients to diversify the payment risk, and patients' limited ability to pay, access to and affordability of such treatments for both patients and society at large is a serious challenge despite the promising technological advancement. Affordability issues limit the benefits of the new technology, which in turn impacts medical innovation, population health, and equitable access to care. Payers seek to mitigate risks such as treatment failure, waning efficacy, and are wary of lack of evidence for efficacy and durability of outcomes[3]. Manufacturers, on the other hand, are keen to gain access to coverage and hence are interested in new payment arrangements[4]. Value-based arrangements, often designed as outcomes-based contracts (OBCs), are gaining greater attention and focus as a mechanism by which payers can ensure access to cutting edge pharmaceutical technologies and treatments. The Centers for Medicare & Medicaid Services (CMS), the administrative arm of the two largest public insurance programs for the elderly, disabled, and low-income people in the US, is entering this arena with the recent announcement of the Cell and Gene Therapy (CGT) Access Model[5], a voluntary model that will engage state Medicaid programs and manufacturers to help make selected therapies more accessible to eligible Medicaid enrollees. We examined the growth in the CGT pipeline, key cost features of CGTs, and the current available payment vehicles for value-based payment/financing of such treatments and provide thoughts on the challenges and potential solutions anticipated with the large inflow of such treatments in the upcoming decades.

Types of cell and gene therapies

CGTs encompass a range of technologies. Gene therapy involves the use of genetic material in the treatment or prevention of disease, and cell therapy involves the transfer of intact, live cells into a patient to help lessen or cure a disease[4]. While only a few dozen CGTs have been approved by the US Food and Drug Administration, ClinicalTrials.gov lists more than 1000 different types of gene therapy in clinical trials, including gene addition, gene correction, gene silencing, reprogramming, and cell elimination, and 8000 active, or actively recruiting, clinical trials for cell therapies, including whole blood transfusion, the transfusion of red blood cells, white blood cells, and platelets, and the transplantation of hematopoietic stem cells to create bone marrow[6].

Costs of cell and gene therapies and the challenges

Cost-related worries about CGTs fall into three types: (a) high cost for a single therapy; (b) high upfront costs; (c) uncertainty about long-term benefits. The high cost of a single therapy reflects not only the high Research and Development (R&D) costs for complex therapies (including the cost of administering clinical trials, some of which fail), but also the relatively low prevalence of the conditions such therapies are meant to treat. For example, ABECMA, the first cell-based gene therapy for adult patients with multiple myeloma approved in 2021[7], has a list price at launch of $419,500[3]. HEMGENIX, the first gene therapy for hemophilia B approved in 2022[8], was priced at around $3.5 million[3]. Lantidra, the first cellular therapy to treat patients with type 1 diabetes approved in 2023[9], was expected to cost $300,000 per patient[10].

While the US is exploring and expanding OBCs for CGTs through public and private insurance programs, Spain and the UK have introduced a national OBC framework, and Germany has similar coverage *via* a sickness fund[3]. While those arrangements aim to balance patient access and affordability to payers, ensure a significant rebate if the drug fails, and mitigates the payer's risk for assuming these costs upfront, payers will still have to deal with upfront costs whether VBP is in place or not, particularly in the US where there is no national/universal healthcare system and the insurance market is fragmented. The lack of universal coverage for continuity of care has posed challenges for payers in multiple ways. First, although the prevalence of these conditions is relatively low or even rare, given the large upfront payment, the budgetary impact is substantial and difficult for even large insurers or state Medicaid programs to plan for and absorb. For example, Casgevy, the first gene therapy to treat patients with sickle cell disease[11], has a list price of $2.2 million for a single course of treatment[12]. Even if only 10% of the current 100,000 sickle cell patients were treated, it could cost $22 billion, not counting new cases over time.

One way to blunt the impact of upfront costs is to establish a value-based payment arrangement, such as a payment model with installments[3,4], so payments can be smoothed out over time. This solution makes it easier for a payer to

absorb the budgetary impact each year. This model hinges on two premises: (a) the long-term benefits can be estimated accurately, and (b) the health benefits would lead to reductions in health care utilization and thus in costs to insurers over time. While the former could be estimated using a reference case – for example, the nonelderly lifetime burden of total medical costs attributable to sickle cell disease is $1.7 million – and the new treatment could be valued at savings in medical costs plus the value of symptom/disease-free years (an improvement in quality of life), the latter is much more difficult given that the payer may not be able to accrue all the potential savings over the insured's lifetime. The U.S. healthcare system is fragmented with many public and private health insurance plans: Medicaid for qualifying low-income populations, Medicare for aged populations and individuals with qualifying disabilities, many employer-sponsored group insurance plans, and the federally facilitated and state-based Marketplace solutions. Moving among insurance plans is the norm rather than an exception for the non-elderly. It is unlikely that a young sickle cell patient cured by a particular therapy while on a given insurance plan would stay with that plan for a lifetime; hence it is impossible for an insurance company to use lifetime benefits to calculate an installment payment, and the reduction in utilization and costs would be significantly discounted due to discontinuity in enrollment. This would in turn increase the pressure on premium growth and render the insurance market less stable if insurance plans were required to cover those therapies.

There have been other value-based payment models proposed to provide coverage for CGTs and prescription drugs, for example, "risk pools, reinsurance, price-volume agreements, expenditure caps, subscriptions, outcomes-based payments and rebates, warranties, population outcomes-based agreements, and coverage with evidence development,"[3,13] However, if an insurer such as Medicaid cannot recoup health benefits over time due to patients exiting the program, the long-term impact on financial sustainability and actuarial soundness is questionable. On the other hand, if the innovator does not receive continued payments, the incentive for innovation will be greatly reduced. Furthermore, many other factors may affect real-world effectiveness and hence complicate long-term benefit valuation.

A thought on an alternative model

Given the fragmented healthcare system, we think a publicly funded special plan with OBCs for CGTs may help address the problem of the fractured insurance market. This special

Table 1. Similarities and differences in the challenges and solutions for financing cell and gene therapies among US and European healthcare systems.

	US healthcare system	European healthcare systems
Common challenges	(a) high cost for a single therapy; (b) high upfront costs; (c) uncertainty about long-term benefits.	
Differences in challenges	Fragmentation of insurance policies, heterogeneous population, difficulty in recouping the benefits of treatments by payers	Smaller patient population size, difficulty in diversifying risks
Advantages	Larger patient population size, better opportunities to pool risks	Universal coverage with a single payer to provide and recoup the benefits
Common themes of solutions	Value-based contracting (OBC) with an emphasis on outcomes	
Different themes in solutions	Early models mostly developed by private manufactures to increase coverage and access. CGTs have also been a part of pharmaceutical company portfolios to position themselves at the forefront of industry advancements for market dominance and monopoly profits.[1]	National focus by Italy, Spain, UK, and France, activities at the sickness fund level in Germany[2]
Newer solution proposed by the US federal government	Cell and Gene Therapy Access Model by the CMS, a voluntary model that will engage state Medicaid programs and manufacturers to help make selected therapies more accessible to eligible Medicaid enrollees. CMS and pharmaceutical manufacturers negotiate a set of key terms, and state Medicaid agencies decide whether to sign the negotiated contract.[3]	N/A
Specific solutions by Horrow & Kesselheim	(a) risk spreading, (b) capping costs based on expected volume, and (c) performance-based models.[4] Subject to the size of risk pools and the limitation in real-world evidence.	Can be adopted across healthcare systems.
Recommended publicly funded special plan	This special plan will pool funds from public sources, with a matching scheme between the federal and state governments, to support the payment for these therapies. A private insurance company that agrees to "buy in" to the treatment and pay a certain fee upfront would need to pay amortized benefits per annum (e.g. expected cost savings due to treatments) should its enrollee receive such a treatment. The federal government and pharmaceutical manufacturers negotiate a set of key terms. Can maximize the risk pool and take advantage of population-based estimates of health benefits.	Can be expanded by including NGOs, philanthropic institutions, and big companies who self-insure for US taxpayers around the globe. Such collaboration can begin with the discovery phase of the treatment to risk-pool the failure of drug trials, hence lower the R&D costs the manufacturer must recoup.
Considerations of insurance company's financial liabilities and premium in the publicly funded special plan	Using a pay-as-you-go system, the financial liabilities borne by the insurance company are limited to the government-determined stream of amortized benefits of the treatment minus a regulatorily-set percentage. Premium will be a regulatorily-set percentage of the government-determined stream of amortized benefits of the treatment.	N/A

Legend: [1]Pharmaceutical-Technology.com. Cell & gene therapy in the pharmaceutical industry: analyzing innovation, investment and hiring trends. Available https://www.pharmaceutical-technology.com/data-insights/cell-gene-therapy-in-pharma/?cf-view. [2]Nazareth T, Ko JJ, Sasane R, Frois C, Carpenter S, Demean S, Vegesna A, Wu E, Navarro RP. Outcomes-based contracting experience: research findings from U.S. and European stakeholders. *J Manag Care Spec Pharm*. 2017 Oct;23(10):1018-1026. [3]Centers for Medicare & Medicaid Services. Cell and gene therapy (CGT) access model. (https://www.cms.gov/priorities/innovation/innovation-models/cgt) [4]Horrow C, Kesselheim AS. Confronting high costs and clinical uncertainty: innovative payment models for gene therapies. *Health Aff (Millwood)*. 2023 Nov;42(11):1532-1540.

plan will pool funds from public sources, with a matching scheme between the federal and state governments, to support the payment for these therapies. A private insurance company that agreed to "buy in" to the treatment and pay a certain fee upfront would need to pay amortized benefits per annum should its enrollee receive such a treatment. By doing so, the access to and affordability of the therapies can be improved for both patients and single insurance plans, and the special plan can adjust the annual amortized payments given updated real-world evidence on effectiveness. The special plan bridges gaps among private/public insurance plans by providing additional benefits that current private or public plans either cannot feasibly estimate due to truncation of coverage or are otherwise unable to provide, and the collective nature of a public model for CGT payment will enable all payers to benefit from centralizing the administrative costs associated with managing and monitoring the contract. Using a pay-as-you-go system, the financial liabilities borne by the insurance company are limited to the stream of amortized values of the treatment determined by the government. Premium will cover the upfront administrative costs by the insurance companies. Table 1 shows the detailed features of the challenges and solutions.

Conclusion

In conclusion, while CGTs offer promise for those difficult-to-treat and rare conditions, the fragmented insurance market and uncertain long-term benefits may discourage adoption of the technology. Innovative approaches in value-based payments are needed to bridge gaps in insurance coverage and link the outcomes with payment to improve market efficiency and health for millions of Americans.

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James X. Zhang
Health Care Evaluation Research, NORC at the University of Chicago, 55 East Monroe Street, 20th Floor, Chicago. IL 60603
zhang-xuejie@norc.org

Lisa R. Shugarman
Health Care Programs, NORC at the University of Chicago

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