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In the Spotlight

Ensuring patient access to gene therapies for rare diseases: Navigating reimbursement and coverage challenges

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The rapid transformation in rare disease treatment, driven by advances in genetic medicine and diagnostics, underscores the urgent need for access to these innovative therapies. With over 10,000 identified rare diseases globally, 80% of which are genetic, the current therapeutic landscape indicates that only 5% of these conditions have FDA-approved treatments. This article examines the critical logistical challenges in commercializing and paying for gene therapies for rare diseases. It highlights the importance of considering innovative payment models, addressing patient portability issues, and aligning payer coverage policies with FDA-approved indications. It emphasizes the need to account for the broader value of gene therapies, incorporate input from disease-specific clinical experts in payer coverage decisions, and reduce administrative barriers to coverage. By adopting a multifaceted approach, we can foster a more supportive environment for the sustainable delivery of gene therapies, significantly improving the lives of patients with rare genetic disorders while rewarding and driving continued innovation.

INTRODUCTION

The treatment of rare diseases is undergoing a rapid transformation, driven by advances in genetic medicine and diagnostic capabilities. With over 10,000 identified rare diseases, the need for innovative therapies has never been more urgent.[1] Approximately 80% of these conditions are genetic in origin, and nearly 85% have prevalences of fewer than 1 in 1,000,000 persons.[2,3] Despite the significant unmet medical need, only 5% of rare diseases currently have FDA-approved therapies.[4] The emergence of precision genetic medicine offers new hope, presenting the potential to address the root causes of serious genetic disorders and potentially alter disease trajectories.

The development and commercialization of gene therapies for rare diseases present unique challenges that extend beyond scientific hurdles. One-time infusion necessitates a one-time upfront payment, but this disrupts our current reimbursement system established for chronic-dosed therapies. Often, gene therapy targets a rare disease where limited or no treatments currently exist, which exacerbates payer challenges due to an evolving understanding of both new disease areas and technologies. Payers face growing concerns about the ability to absorb the upfront costs, leading to access barriers for patients.

In order to unlock the full potential of gene therapies for rare diseases, a multifaceted approach is needed to address the challenges in both development and access. While acknowledging the added impact of regulatory barriers,[5] this article explores various payment policy solutions, strategies to mitigate patient portability issues, and approaches to align payer coverage policies with FDA-approved indications. Additionally, it emphasizes the importance of considering value beyond durability, involving disease clinical experts and patients with lived experience in coverage decisions, and reducing administrative barriers to ensure timely access to care.

ENSURING PATIENT ACCESS

For gene therapies in the rare disease space, FDA approval is only the first step to patient access. Once approved, access hinges on coverage by both public and private health insurers, with varying coverage policies.

To ensure patients will be able to access this new era of medicine, it is critical to address the following challenges.

One-time, upfront costs: the cost of gene therapies is incurred at the time of administration for durable effects over time. Conversely, traditional chronic treatments are paid incrementally with each infusion or refill. While gene therapy may cost less than a lifetime of standard chronic therapies and achieve significantly better outcomes,[6] the single upfront cost may be burdensome for payers. For example, Roctavian (valoctocogene roxaparvovec) has an upfront cost of over $2 million dollars. However, the current cost of care for a patient with severe hemophilia A can range from over 20 to 100 million dollars in a lifetime depending on the age of diagnosis.[7] Because payers may not fully appreciate the cost effectiveness of one-time treatment, they are increasing premiums and deductibles, excluding coverage of gene therapies, or encouraging their beneficiaries to seek assistance from manufacturer-sponsored patient assistance programs.

Limited long-term health outcome and economic data at the time of product approval: gene therapies are transformative and can reduce overall healthcare costs. However, particularly given the newness of the technology, it takes years

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of monitoring treated patients to verify the anticipated long-term durability and other clinical, societal, and economic benefits.

Patient portability: individuals in the United States regularly change insurance plans— when moving to a new job, acquiring plan eligibility through a family member, purchasing plans on the marketplace, etc. Therefore, a payer is unlikely to receive the full benefit of reduced total cost of care for covering a one-time gene therapy. While patient portability is not unique to gene therapy, the issue is exacerbated due to the upfront cost and the expectation of health system savings over a patient's lifetime.

Restrictive coverage parameters: payers determine coverage policies using many different data sources. These include clinical compendia recognized by the Centers for Medicare and Medicaid Services (CMS), clinical trial data, and FDA prescribing information. Some payers adopt narrow clinical trial inclusion/exclusion criteria that were represented in the pivotal clinical trial vs. using the FDA-approved indication.[8] This practice undermines FDA's authority in determining safety and efficacy. Such a practice is also inappropriate in the case of state Medicaid programs that, along with their contracted managed care organizations (MCOs), are required by federal statute to authorize treatment for cell and gene therapies (CGTs) when they meet the definition of a covered outpatient drug and are prescribed for their FDA-approved medically accepted indication.[9,10] Additionally, before allowing coverage, some insurers utilize formulary management tools like prior authorization or require functional testing that lacks robust evidence.[11] Payers are using patient frailty or function (based on ECOG, Karnofsky/Lansky scores, and the 6-min walk test) as a proxy measure for authorization criteria. Unless stated in the FDA-approved indication statement, restrictions based on gene status, age, disease severity, or any other measure should not be used by payers as authorization criteria. CGTs approved via accelerated approval are labeled by some payers as experimental/investigational. Combined, these coverage policies only serve to undermine FDA's gold standards of safety and efficacy, requiring physicians to file burdensome appeals and causing inequities and delays in patient access.[12,13]

Inconsistent payment methodologies: reimbursement methods for rare disease gene therapies vary by administration route and care setting. States utilizing all patient refined diagnosis-related groups (APR-DRGs) establish the base payment on a hospital-specific basis, while states using Medicare severity diagnosis-related groups (MS-DRGs) may establish a baseline using CMS standardized amounts.[14] Additionally, some payers utilizing APR-DRGs have outlier thresholds. Inpatient gene therapy is typically covered under a bundle payment, and outpatient gene therapy is covered separately. Some states treat traditional bundled drugs as outpatient and then collect the mandatory Medicaid rebate on these treatments. For newly FDA-approved CGTs, some state Medicaid programs are delaying coverage until a unique product-specific HCPCS J-code is issued (even though using a miscellaneous HCPCS J-code with the CGT's NDC code is common billing practice). Similarly, some state Medicaid programs delay access until a drug's NDC is listed in the Medicaid rebate file. Both approaches only serve to delay access while a patient's disease irreversibly progresses. The complex patchwork of payment systems and varied billing practices requires extensive time and resources to navigate, contributing to access delays after FDA approval that can adversely affect patient outcomes.[15]

Medicaid access across state lines: gene therapies for rare diseases are often administered at limited designated centers of excellence, requiring patients to travel from out of state to receive care. For patients with Medicaid coverage, their home state pays for treatment. Barriers and inefficiencies can result while out-of-state providers obtain necessary treatment authorizations from home-state Medicaid programs; providers must also ensure that they will be properly reimbursed for the services provided. All of this creates unnecessary delays. Without assistance, the accumulation of significant non-medical costs, like lodging and transportation, can also financially burden families.

There are many proposed solutions to these challenges, requiring redesigning the annual commercial and Medicaid coverage and payment policies to better accommodate the CGT pipeline.

Establish CGT pipeline forecasting: creating a standardized communication mechanism for all states to preview gene therapies coming to market would allow states to appropriately and preemptively budget soon-to-be approved CGTs.[8] Collaborating closely with drug developers can provide insights into the anticipated patient populations and help inform the upfront costs on state budgets requests, ensuring long-term sustainability and patient access.

Pursue value-based payment models, where possible: innovative payment arrangements that would not require payers to cover the entire cost of a gene therapy upfront include installment plans, subscription agreements, outcomes-based agreements (OBAs), and warranties.[16] However, Medicaid programs must adhere to annual budget constraints and cannot typically engage in multi-year payment plans unless they are tied to outcomes through an OBA. Alternatively, they may negotiate a subscription agreement, where insurers pay a fixed price to cover a therapy for a defined population with potential reduction for any patients exceeding a threshold. Innovators may seek a warranty if a CGT is not as durable as expected or results in adverse outcomes, such as hospitalization. Under such arrangements, the developer might provide a rebate to the payer, the payer would not be obligated to make future payments, or the developer could pay for a patient's use

of additional healthcare services. To test innovative Medicaid payment models, the Center for Medicare and Medicaid Innovation (CMMI) launched the CGT access model, focusing on sickle cell disease.[17] It will be important to assess the findings and federal savings associated with this pilot before CMMI expands the pilot's scope to other disease areas. Importantly, the viability of OBAs is very much a function of a specific therapy and the disease it is intended to treat. For one, it is not always clear whether reliable outcome metrics can be readily collected and interpreted outside of a clinical setting, and establishing practical time frames is difficult for diseases with small patient populations and slow, highly variable disease progression.

Employ financial-based tools: reinsurance plays a crucial role in mitigating financial risk across the insurance industry by allowing primary insurers to transfer a portion of their risk to reinsurers; especially for high-cost gene therapies, reinsurance can spread potential losses across multiple entities. Payers can also participate in stop-loss reinsurance to provide protection against claims that, in aggregate, are in excess of expected losses.[16] Another potential solution is for the federal government to partner with states: options include creating a new drug benefit for CGTs or increasing the federal medical assistance percentage (FMAP) coverage for CGTs in state Medicaid programs.[8]

Consider value beyond durability: the total indirect and non-medical cost of rare diseases is estimated at $548 billion annually ($64 billion for children and $484 billion for adults).[18] Absenteeism accounts for nearly $150 billion (27%), followed by presenteeism ($138 billion, 25%) and forced retirement ($136 billion, 25%). For adults, caregiver absenteeism costs match those of individuals with rare diseases ($64 billion vs. $60 billion), while for children, caregiver absenteeism costs may exceed those of the affected child ($89 billion vs. $60 billion).[19] There is a need for nuanced evaluation of disease-specific treatment durability and broader impacts on quality of life when assessing the value of a gene therapy beyond what is included in traditional health technology value assessments.[20] These treatments can affect patients' and families' well-beings in ways that have significant societal and economic benefits. Parents or caregivers may be able to return to work, reducing lost productivity and increasing workforce participation. Children may experience fewer school absences and participate in everyday childhood activities (such as organized sports or riding a bicycle), expanding their educational opportunities and future potential. Healthcare system savings can be substantial due to reduced hospitalizations and long-term care needs. Luxturna (voretigene neparvovec-rzyl), a gene therapy to treat inherited blindness, provides an apt example. The multi-luminance mobility test (MLMT) was a completely new test developed hand in hand with FDA regulators after investigators noted improvements in patients' ability to navigate in dim light.[21] This functional improvement, while not captured by traditional clinical measures, represents a meaningful enhancement in patients' daily lives, independence, and overall well-being. It is imperative for payers to involve clinicians with direct experience treating the disease, and patients with lived experience, in coverage policy development to understand the full scope of a therapy's value and ensure payers are making patient-centric decisions.

Utilize portability mitigation strategies: risk-pooling strategies, where multiple payers contribute to a shared fund for high-cost therapies, can distribute financial burdens more equitably. Mortgage models offer another approach, amortizing costs over time with subsequent insurers assuming payments if patients change plans. These models can incorporate portability mechanisms, allowing the initial payer's investment to follow the patient. While each model has limitations, they aim to better align payer incentives with patient outcomes and therapy value.

Align payer coverage policies with FDA-approved indication: FDA reviewers carefully consider the generalizability of the scientific evidence, consistencies in disease process across different groups, and a drug's overall benefits and risk in determining the patient population appropriate for treatment.[22] Therefore, all payers should uphold FDA's authority in determining the safety and efficacy of medical products, including accelerated approval drugs, and cover the entire population included in the gene therapy's "indication and usage" section of the prescribing insert. CMS should establish a public dashboard to track coverage policies, denials, complaints, and reimbursement issues while issuing guidance to ensure state Medicaid programs and their contracted MCOs cover FDA-approved, medically accepted indications. States should enforce clear timelines and escalation procedures for denials, and self-insured employers must disclose excluded genetic conditions or therapies to employees before enrollment.

Uphold physician authority in determining medical necessity: physician specialists are experts in their field, spending years in training, research, and clinical practice. Payers should consult these experts in developing coverage policies to ensure alignment with therapeutic area understanding and clinical practice. Specialists should also be included in external reviews.

Remove unnecessary administrative barriers to ensure timely access to care: administrative hurdles pose real barriers to accessing timely treatment. To mitigate coverage delays, CMS should issue guidance to all state Medicaid programs to use the miscellaneous HCPCS J-code to process claims until a unique product-specific HCPCS code is available and reinforce that, upon FDA approval, a drug is considered a covered outpatient drug and should be covered by state Medicaid programs and their contracted MCOs. To streamline Medicaid payment and facilitate enrollment of out-of-state providers in another state's Medicaid program, federal legislators are advancing the Accelerating Kids' Access to Care Act.[23] Whether through that legislation or another approach,

federal action will likely be required to help smooth treatment barriers between states.

Allow developers to provide certain ancillary support: the creation of federal safe harbors provides legal certainty that developers can offer limited support programs to patients and caregivers who must travel to specialized treatment facilities.[24] This precedent was set with Kymriah (lisocabtagene maraleucel) to allow the manufacturer to offer travel and lodging assistance.[25] By reducing financial challenges for patients and their families, federal safe harbors alleviate a significant barrier to accessing these potentially curative but logistically complicated therapies.

CONCLUSION

The emergence of gene therapies for rare diseases presents unique challenges in both development and patient access. This article has highlighted key barriers impacting patients' ability to access approved gene therapies and offers practical, multifaceted solutions to unlock the full potential of these innovative treatments. By addressing these challenges comprehensively, we can create a more supportive environment for the development and sustainable delivery of gene therapies, ultimately improving the lives of patients with rare genetic disorders and forever changing the trajectory of disease.

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Conceptualization, writing, review, and editing, D.B., C.H., L.K., and J.L.; writing support, review, and editing, C.M.; project administration: C.K.M.

DECLARATION OF INTERESTS

D.B. is an employee and shareholder of Sarepta Therapeutics. C.H. is an employee and shareholder of Sarepta Therapeutics. L.K. is an employee and shareholder of Ultragenyx Pharmaceutical. J.L. is an employee of DK Pierce. C.M. is an employee of King and Spalding. C.K.M. is an employee of the American Society of Gene and Cell Therapy.

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