



January 22, 2024

Senator Bill Cassidy, M.D.
Ranking Member
U.S. Senate Committee on Health, Education, Labor and Pensions
428 Senate Dirksen Office Building
Washington, DC 20510

Dear Ranking Member Cassidy,

On behalf of the more than 30 million Americans living with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) is pleased to comment on your request for information (RFI) titled “Improving Americans’ Access to Gene Therapies.”

NORD is a unique federation of non-profit and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing this landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to safe and effective diagnostics and therapies.

For many patients and families affected by rare diseases, gene therapies offer the unique hope of a cure for debilitating and often fatal diseases. Indeed, five of the seven gene therapies approved by the FDA in 2023 are for rare diseases.¹ Unfortunately, coverage and reimbursement issues for gene therapies often lead to a delay or denial of coverage, in large part due to the high up-front cost of the therapy, as well as payers’ questions about long-term safety and efficacy.² In light of current data gaps and the rapidly evolving gene therapy landscape, NORD recognizes the need for more transparent and comprehensive data to better understand current and future barriers to patient access. We would like to thank you for commissioning this RFI and appreciate the opportunity to provide the rare disease perspective. Specifically, we would like to address the following three questions in the RFI.

¹ Slabodkin, Greg. (2024). Gene Therapy Approvals Expected to Ramp Up in 2024 Amid Manufacturing, Cost Challenges. *BioSpace*. <http://tinyurl.com/mtvh74vm>

² Allen, J., Berry, D., Cook, F., Hume, A., Rouse, R., Srirangam, A., Wellman, J., & McCombs, C. (2023). Medicaid coverage practices for approved gene and cell therapies: Existing barriers and proposed policy solutions. *Molecular therapy. Methods & clinical development*, 29, 513–521. <https://doi.org/10.1016/j.omtm.2023.05.015>

How should lawmakers define an “ultra-rare” disease or disorder cell or gene therapies should be eligible for inclusion in new coverage or contracting requirements for those patients with an ultra-rare disease or disorder? What definitions should lawmakers consider?

NORD strongly urges against setting a precedent for treating “ultra-rare” conditions differently from other rare diseases. Specifically, we believe that the current definition of rare disease is appropriate, and that attempts to bifurcate the rare community could create regulatory uncertainty and damage existing incentive structures. For 40 years, the United States has defined a rare disease as “a disease or condition that affects less than 200,000 people in the United States”³ and this definition continues to be as relevant today as it has always been. Rare disease drug development programs share the same fundamental challenges associated with small patient populations, heterogenous clinical manifestations, and poorly understood disease biology, thus requiring specialized tools and incentives. In fact, how well the disease pathophysiology and underlying mechanism of action is understood, or how homogenously the disease tends to progress over time can have a much bigger impact on the complexity of the drug development program than the exact size of the affected patient population. At its core, rare disease research is riskier, and more time consuming and expensive than for more common diseases, regardless of the specific disease prevalence. Moreover, NORD questions the practicality of the proposal for three key reasons:

- 1. Any “ultra-rare” disease prevalence cut-off is inherently arbitrary and creates unpredictability that risks damaging rare disease drug development.** Prevalence estimates for rare diseases are inherently imprecise, as demonstrated by the great variability in prevalence estimation approaches and estimates incorporated in FDA rare disease designations. This is often particularly true for the diseases with lowest prevalence where each patient’s data has a particularly large impact on summary estimates.
- 2. NORD is concerned that the creation of an “ultra-orphan” definition could lead to perverse incentives and gamesmanship.** As mentioned above, disease prevalence estimates are inherently imprecise. In fact, as awareness of and testing for a rare disease increase, for instance because a new drug is being developed, the prevalence estimates often increase.⁴ Creating an additional sub-class of rare diseases based on prevalence estimates may create disincentives for efforts to raise awareness and improve timely diagnosis while the drug is under development. Moreover, such policy could create incentives for “salami slicing”, the practice of artificially subdividing patient groups so that prevalence estimates may fall below a specified threshold.⁵ FDA has previously recognized the danger of encouraging salami

³ U.S. Food and Drug Administration. (2022). Rare Diseases at FDA. *FDA.gov*. <http://tinyurl.com/mr2tnmc9>

⁴ Stéphane Auvin, John Irwin, Paul Abi-Aad, Alysia Battersby. (2018) The Problem of Rarity: Estimation of Prevalence in Rare Disease. *Value in health*, 21. 501-507, <https://doi.org/10.1016/j.jval.2018.03.002>.

⁵ Gibson, S., & von Tigerstrom, B. (2015). Orphan drug incentives in the pharmacogenomic context: policy responses in the US and Canada. *Journal of law and the biosciences*, 2(2), 263–291. <https://doi.org/10.1093/jlb/lsv013>

slicing and has promulgated regulation to clarify when a product may or may not qualify for orphan drug incentives.⁶

- 3. Treating access to some therapies differently simply based on the size of the currently known patient population is arbitrary and capricious, and risks further exacerbating health inequities.** Simply how common a rare disease is, or how common it is believed to be, should not determine who can have access to a life-altering therapy. Insurance coverage is vital to access, and limiting access simply based on prevalence estimates sets a dangerous precedent that may have far-reaching ramifications for the broader health care ecosystem.

Manufacturers make future drug development pipeline decisions based on present information; if contracting terms for value-based arrangements are perceived to prioritize the wrong factors, decision making could shift in favor of an arbitrary distinction that is not in the best interest of patients or public health, ultimately causing potentially irreparable harm to rare disease drug development.

How do patient populations currently access and pay for these therapies? What, if any, are the cost-sharing mechanisms that patients are typically subject to when paying for and accessing these therapies?

The currently approved rare disease gene therapies span patient populations that are heterogenous across age, sex, race and insurance coverage, resulting in a widely divergent set of payment models and patient cost sharing requirements. Concerns about patient access to these therapies are heightened given the strong pipeline of gene therapies under development. As a result, spending for gene therapies is likely to skyrocket in future years; in 2024 alone, an estimated 17 gene therapies are likely to seek approval, with many more in the pipeline moving forward.⁷ From 2020 to 2034, it is estimated that the proportion of patients who could become eligible to receive a gene therapy may be comprised of 17.9% minors, 35.4% adults, and 46.7% elderly, suggesting that cost will be spread across both public and private payers.⁸

While some private insurers and state Medicaid programs have begun entering into value-based payment arrangements to help contend with the cost of covering high-cost gene therapies, limited details have been made public. Future coverage determinations and payment mechanisms must consider how to confront the high up-front cost, risk pooling to spread costs over a larger

⁶ Ibid

⁷ Luxner, Larry. (2024) FDA, industry officials predict 2024 will be 'breakout year' for gene therapy approvals. *Rarediseaseadvisor.com*. <http://tinyurl.com/3b3bawyw>

⁸ Wong, C. H., Li, D., Wang, N., Gruber, J., Lo, A. W., & Conti, R. M. (2023). The estimated annual financial impact of gene therapy in the United States. *Gene therapy*, 30(10-11), 761–773. <https://doi.org/10.1038/s41434-023-00419-9>

population size, and clinical performance.⁹ Given the nascency of gene therapies and the limited number of patients that have been treated to date, relatively scarce and fragmented evidence specific to patient access to gene therapies exist. However, anecdotally we know that access trends, patient experiences, and access barriers for gene therapies are likely to closely mirror those for other rare disease therapies with relatively high costs. Certain themes, such as utilization management, prohibitive cost sharing, and access restrictions are common across many rare disease patients, and often heightened for gene therapies. In fact, individual rare disease gene therapies are often only approved for patient populations with narrowly defined age groups, heightening concerns about step therapy, prior authorization, and other utilization management tools that can delay access until the patient ages out of the age group for which the therapy was FDA-approved. Below we provide a summary of patient access barriers by payer types.

1. Access barriers for commercially insured patients

Patients covered by commercial insurance plans are frequently subject to cost-sharing mechanisms and coverage restrictions on high-cost therapies. Though patient experience may differ across plans, similar themes are present across all carriers. Given the limited number of approved therapies and time on the market, using other high-cost products as analogous to gene therapies may provide insight into broader patient experience on access.

In the private insurance market, payment for products in the top quartile of annual cost (\$175,271-\$905,556) are over 85% more likely to impose coverage restrictions on the product than for a lower cost therapy.¹⁰ Step therapy is one way that plans attempt to reduce access to higher cost products, such as gene therapies. Of the 18 largest commercial health plans that cover specialty drugs and products, 14 require the patient to “fail” on a less expensive medication before advancing to a more expensive medication.¹¹ While this may save money for the payer, step therapy protocols frequently hurt and delay access to needed therapies for patients. Several studies have found that other utilization management protocols, such as prior authorization, increase time to treatment initiation, in one study ranging from 3.6 days for cancer drugs to 31 days for RA and IBD drugs.¹² The resulting delay caused a 26% reduction in treatment initiations in some specialties.¹³

⁹ Horrow, Caroline., Kesselheim, Aaron. (2023). Confronting high costs and clinical uncertainty: innovative payment models for gene therapies. *Health affairs*, 42(11), 1477-1621. <https://doi.org/10.1377/hlthaff.2023.00527>

¹⁰ Chambers, James., Panzer, Ari., et. Al. (2019) Variation in US private health plans’ coverage of orphan drugs. *The American journal of managed care*, 25(10). <https://www.ajmc.com/view/variation-in-us-private-health-plans-coverage-of-orphan-drugs>

¹¹ Clifford, Katherine., Beinfeld, Molly et.al. (2023). How might US health plans cover gene therapies for sickle cell disease? Insights from the SPEC database. *CEVR*. <https://cevr.tuftsmedicalcenter.org/news/how-might-us-health-plans-cover-gene-therapies-for-sickle-cell-disease-insights-from-the-spec-database>

¹² Ismail, W. W., Witry, M. J., & Urmie, J. M. (2023). The association between cost sharing, prior authorization, and specialty drug utilization: A systematic review. *Journal of managed care & specialty pharmacy*, 29(5), 449–463. <https://doi.org/10.18553/jmcp.2023.29.5.449>

¹³ Ibid

Coverage restrictions may also include subgroup restrictions that go beyond the FDA approved label. While orphan therapies are approximately twice as likely as non-orphan therapies to have sub-group restrictions imposed, the issue is even greater for gene therapies.¹⁴ For instance, for commercially insured sickle cell patients, 15 of the 18 largest insurers have subgroup restrictions more stringent than the FDA label.¹⁵ Similarly, a number of insurers have imposed restrictions exceeding the FDA label for a high-cost spinal muscular atrophy gene therapy, such as reducing the age of eligibility, demonstrating symptoms of the disease before a specified time, or having other biomarkers that restrict eligibility beyond what the FDA has deemed safe and effective.¹⁶ Coverage restrictions beyond what is on the label hurt patients by denying them the clinically indicated drug recommended by their physician.

Beyond coverage restrictions, commercially insured patients may be subject to exorbitantly high deductibles or co-insurance amounts. Amongst patients suffering from cancer or multiple sclerosis, two targets for gene therapies approaching the market, out-of-pocket spending was 25 and 32 times greater respectively than for patients with no deductible or co-insurance claims.¹⁷ Given that a co-insurance scales with the price of the product and the formulary placement of the product, gene therapies could simply be out of reach for many commercially insured patients with co-insurance. Conversely, co-insurance on high-cost medications such as gene therapies could present a problem of adverse selection for plans that offer more limited cost sharing arrangements, such as co-pays. Co-insurance on gene therapies presents actuarial risk for the industry as a whole.

2. Access barriers for Medicaid patients

While Medicaid is obligated to cover every FDA approved therapy to the label, so long as the manufacturer participates in the Medicaid Drug Rebate Program (MDRP), restrictions on access are often greater than FDA recommended limitations.¹⁸ Medicaid patients frequently suffer from lack of timely access to care, which may result in negative, but avoidable outcomes.¹⁹ In pediatric populations, delays in access to crucial gene therapies can result in the patient “ageing out” of the indication on the label. Across a survey of 16 states, 14 states had more restrictive coverage requirements than on the FDA label for a high-cost spinal muscular atrophy drug,

¹⁴ Jenkins, N. B., Rucker, J. A., Klimchak, A. C., Sedita, L. E., & Chambers, J. D. (2023). Commercial health plans use of patient subgroup restrictions: An analysis of orphan and US Food and Drug Administration-expedited programs. *Journal of managed care & specialty pharmacy*, 29(5), 472–479. <https://doi.org/10.18553/jmcp.2023.22363>

¹⁵ Ibid

¹⁶ Sullivan, Thomas. (2019). How are insurers treating the \$2M drug, Zolgensma?. *Policymed.com*. <https://www.policymed.com/2019/10/how-are-insurers-treating-the-2m-drug-zolgensma.html>

¹⁷ N.A. (2023) Faced with high cost sharing for brand medicines, many commercially insured patients with chronic conditions use manufacturer copay assistance. *Phrma.org*. <https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/D-F/Faced-with-High-Cost-Sharing-for-Brand-Medicines.pdf>

¹⁸ Allen, J. et.al. Medicaid Coverage Practices. <https://doi.org/10.1016/j.omtm.2023.05.015>

¹⁹ Gray S. J. (2016). Timing of Gene Therapy Interventions: The Earlier, the Better. *Molecular therapy: the journal of the American Society of Gene Therapy*, 24(6), 1017–1018. <https://doi.org/10.1038/mt.2016.20>

which must be administered to patients under the age of 2.²⁰ Restrictions included lower age requirements, severity of condition thresholds, and limitations in the use in populations not included in the clinical trial, even if use in the population is indicated on the label.²¹ Further restrictions than the label are particularly concerning because SMA can present as asymptomatic at a young age, with symptoms only arising when the patient ages out of eligibility for treatment.²²

Similar to the commercial population, state Medicaid programs are not monolithic in their approach to covering gene therapies. While state Medicaid programs are required to cover all FDA approved products, the patient interaction with the payer may vary depending on whether the state has contracted with a Managed Care administrator. A number of states who have elected to run their Medicaid program through an MCO have elected to “carve out” a subset of the pharmaceutical benefit, particularly impacting high-cost drugs, and pay for the high-cost products under FFS.²³

An additional challenge facing Medicaid patients is the location of centers that are able to administer gene therapies. Given the complexity associated with the administration of gene therapies, only a small subset of health care facilities across the country have the ability to offer gene therapies to patients.²⁴ Out of state travel is particularly acute in the rare disease community. A 2019 study of rare disease patients and caregivers found that 39% of respondents had previously traveled more than 60 miles to receive care, and 17% had moved (or considered relocating) in order to be closer to care.²⁵ In addition to the financial complexities associated with families needing to cross state lines to seek care, including time off of work, childcare, and other travel expenses, many patients’ home state requires the out of state provider to complete an exhaustive and byzantine set of credentialing paperwork. On top of the paperwork cost associated with out of state credentialing, the response time from the home state can vary wildly. One proposed solution to this issue is the Accelerating Kids’ Access to Care Act (H.R. 4758), which would create a voluntary federal pathway which states could opt into to streamline the credentialing process.

²⁰ Allen, J. et.al. Medicaid Coverage Practices. <https://doi.org/10.1016/j.omtm.2023.05.015>

²¹ Ibid

²² Sullivan, Thomas. (2019). How are insurers treating the \$2M drug, Zolgensma?. *Policymed.com*. <https://www.policymed.com/2019/10/how-are-insurers-treating-the-2m-drug-zolgensma.html>

²³ Gifford, Kathleen., Winter, Anne., Wiant, Linda., et. Al. (2020) How state Medicaid programs are managing prescription drug costs. *KFF*. <https://files.kff.org/attachment/How-State-Medicaid-Programs-are-Managing-Prescription-Drug-Costs.pdf>

²⁴ ASCGT. (2023) Gene therapy centers. *ASCGT*. <https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-centers>

²⁵ National Organization for Rare Disorders. (2019) Barriers to rare disease diagnosis, care and treatment in the US: a 30-year comparative analysis. *Rarediseases.org*. https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf

3. Access barriers for Medicare patients

Medicare covers nearly 19% of Americans, a number which is expected to grow as the population ages, and rare disease patients benefit from life-extending transformative therapies.²⁶ Coverage of gene therapies falls under Medicare Parts A and B, or the Medicare Advantage equivalent. Cost-sharing for gene therapies is not homogenous across the population, however. Individuals enrolled in original Medicare are liable for up to their deductible during each hospital benefit period in Medicare Part A, and a flat 20% co-insurance amount in Medicare Part B. As such, original Medicare patients can be subject to tremendously high levels of cost sharing for gene therapies, the likes of which they may be unable to afford with or without Medicare Supplement Insurance (Medigap).

Access under Medicare Advantage works differently, depending on the plan structure. While some beneficiaries may only have a co-pay, other beneficiaries may be subject to co-insurance, though Medicare Advantage beneficiaries have an annual out-of-pocket maximum for Parts A and B covered services.²⁷ Out-of-pocket caps can dramatically reduce patient exposure to high out-of-pocket cost.

Reducing barriers to access for patients

Broadly, improving patient access to gene therapies across payer types relies on three approaches: reducing utilization management barriers, reducing cost-sharing and ensuring therapies are covered to the FDA approved label. Gene therapies are life-changing for the most vulnerable patients and attempts to restrict access are directly correlated with worse health outcomes and, in many cases, increased healthcare cost compounded over the life of the patient. Even though gene therapies have high up-front costs, patients should not suffer because of the United States' fragmented payment and reimbursement system.

One consideration for policymakers is to identify lessons learned from the coverage of end-stage renal disease (ESRD) in Medicare. Treatment of ESRD historically tracked similarly to gene therapies. Prior to the inception of Medicare coverage for all eligible ESRD patients, regardless of age, in 1973, treatment was limited to a very small number of patients due to high cost and limited availability of dialysis machines.²⁸ Today, for those under typical Medicare age, initial coverage of ESRD treatment costs is mandated by the individual's primary insurer for the first 30 months, after which the patient becomes Medicare eligible.

²⁶ Keisler-Starkey, Kathleen., Bunch, Lisa., Lindstrom, Rachel. (2023) Health insurance coverage in the united states: 2022. *Census.gov*. <https://www.census.gov/library/publications/2023/demo/p60-281.html#:~:text=Between%202021%20and%202022%2C%20the,in%20uninsured%20rates%20for%20workers.>

²⁷ N/A. (2024) Maximum out-of-pocket limit. *Medicareinteractive.org*. <https://www.medicareinteractive.org/get-answers/medicare-health-coverage-options/medicare-advantage-plan-overview/maximum-out-of-pocket-limit>

²⁸ Eggers P. W. (2000). Medicare's End Stage Renal Disease Program. *Health care financing review*, 22(1), 55–60.

A similar public-private partnership approach may be one approach to covering high-cost gene therapies that could defray the exorbitant cost for private payers and increase access for patients, as Senator Cassidy has previously identified.²⁹ As mentioned previously, many gene therapy contracts involve outcomes-based payments, which scale based on whether certain clinical endpoints are met. Payments for gene therapies can be spread out over a specified time horizon, with predictable levels of spending for all parties involved. In an analogous gene therapy example, private payers could assume the risk for the beginning specified period of time, before Medicare coverage kicks in to defray the cost. Assuming a public private partnership would help to increase access to gene therapies by mitigating the danger of insolvency for smaller insurers and improving downstream outcomes for patients, a net positive for both private insurers and public, when the patient eventually ages into Medicare.

Do physicians or health systems bear any financial risk as part of prescribing a patient with an ultra-rare disease or disorder these therapies? If so, as part of what program or what type of contract?

Alternative payment models for high-cost therapies are constantly evolving. CMS recently announced a new model that would allow state Medicaid agencies to establish a multi-state approach for pursuing and administering outcomes-based agreements.³⁰ Commercial plans are exploring and testing other outcomes-based approaches. Due to the recency of these alternative payment models, however, additional research is necessary into the budgetary impacts and patient access outcomes.

While Medicaid and commercial insurers have increased flexibilities to negotiate outcomes-based contracts with payers, resulting in non-standard reimbursement structure, Medicare is limited to payment through Parts A and B. To standardize payment for services across the board, CMS has created a set of Medicare Severity Diagnosis Related Groups (MS-DRGs, or DRG). Currently, only a single DRG for CAR-T therapies has been included in the Inpatient Prospective Payment System (IPPS), though CMS has announced they are considering an additional DRG for cell and gene therapies.³¹ DRGs are intended to cover the cost of an entire care episode, including hospital administered drugs, inpatient stay time, physician salary, and other costs incurred during the administration of the care episode.

Given the often-exorbitant cost of administering new therapies, hospitals are eligible to receive New Technology Add-on Payments (NTAP), that may help to bridge the gap between the time

²⁹ Cassidy, Bill. (2019) How will we pay for the coming generation of potentially curative gene therapies? *Statnews.com*. <https://www.statnews.com/2019/06/12/paying-for-coming-generation-gene-therapies/>

³⁰ Fowler, Liz., Mitta, Vinod., McWright, Laurie. (2023) CMS innovation center's one-year update on the executive order to lower prescription drug costs for Americans. *Cms.gov*. <https://www.cms.gov/blog/cms-innovation-centers-one-year-update-executive-order-lower-prescription-drug-costs-americans>

³¹ Dworkowitz, Alexander., Fiori, Anthony., Ofengeyem, Yelena. (2023). Accessing cell and gene therapies: insights on coverage, reimbursement, and emerging models. *Jdsupra.com*. <https://www.jdsupra.com/legalnews/accessing-cell-and-gene-therapies-5546106/>

when a new, high-cost therapy is introduced to the market, and when CMS can update the DRG accordingly. NTAPs can reimburse the hospital up to 65% of the relevant DRG, but are typically limited to between two and three years.³²

Unfortunately, the current DRG and NTAP system is ill-equipped to deal with the new reality of individualized medicine and the promulgation of readily accessible gene therapies. Indeed, the existing NTAP system frequently does not cover sufficient reimbursement for new therapies. In 2020, 6 of the 18 FY2020 technologies eligible for NTAP payments may incur hospital losses of greater than \$10,000 per treatment episode, including three with potential losses greater than \$50,000 per treatment episode.³³ The negative economics associated with the administration of new, high-cost therapies serves to create a disincentive for hospitals and health systems to offer these new and transformative therapies.

An additional concern regarding the Medicare bundled payment system is the limited volume of treatments from which to calculate the cost of a care episode. Certain treatments are considerably more common than others, and as such it is easier to calculate an accurate estimate for what a care episode may cost the hospital. Administration of gene therapy, for example, does not fall cleanly into a standardized range of cost outcomes for a myriad of reasons, including the acquisition cost of the drug for the hospital and the variation in resources needed to prepare the patient for administration. As such, Congress should evaluate whether granting Medicare additional flexibility in how it pays for the purchase and administration of gene therapies to best accommodate the actual cost may be useful.

We again thank Senator Cassidy for the opportunity to comment and look forward to working with the Senator to ensure rare disease patients may fully access, and benefit from, transformative gene therapies. For any questions related to this letter, please contact Mason Barrett, Policy Analyst (mbarrett@rarediseases.org) or Karin Hoelzer, Director of Policy and Regulatory Affairs (khoelzer@rarediseases.org).

Sincerely,



Mason Barrett
Policy Analyst
National Organization for Rare Disorders



Karin Hoelzer, DVM, PhD
Director, Policy and Regulatory Affairs
National Organization for Rare Disorders

³² Manz CR, Bekelman JE, Doshi JA. The Changing Characteristics of Technologies Covered by Medicare's New Technology Add-on Payment Program. *JAMA Netw Open*. 2020;3(8) doi:10.1001/jamanetworkopen.2020.12569

³³ Ibid