ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

January 22, 2024

The Honorable Bill Cassidy, MD
United States Senate
455 Dirksen Senate Office Building
Washington, D.C. 20510

Re: Request for Information: Improving Americans' Access to Gene Therapies

Dear Senator Cassidy:

The American College of Medical Genetics and Genomics (ACMG) appreciates the opportunity to provide feedback on your Request for Information on Improving Americans' Access to Gene Therapies. The majority of known rare and ultra-rare diseases are genetic and therefore fall under the expertise of ACMG and the healthcare professionals we represent. The ACMG is a prominent authority in the field of medical genetics and genomics and the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics. As the only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization, the ACMG provides education, resources, and a voice for more than 2,500 clinical and laboratory geneticists, genetic counselors, and other healthcare professionals. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education, and clinical research and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health.

RFI Section: Which Treatments Should Be Included?

1. *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?*
2. *Are there other criteria that lawmakers should consider in determining which therapies should be included in new coverage or contracting models? Examples could include treatment characteristics (e.g. curative treatments or treatments reaching a certain cost threshold) or treatments fitting certain patient profiles (e.g. pediatric patient populations or the fatality of the disease) If so, what definitions should lawmakers consider?*

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Defining ultra-rare:

The World Health Organization (WHO) defines *orphan disease* as a condition that affects less than 6.5-10 per 10,000 people. According to the Food and Drug Association (FDA), a disease is designated orphan status in the United States if it affects fewer than 200,000 people nationwide. This same definition has been used by the FDA to define a "rare" disease. There are currently more than 7000 orphan or rare disorders (https://www.fda.gov/patients/rare-diseases-fda). The rarest of this group have been designated "ultra-rare" disorders. There are multiple definitions of ultra-rare disorders. For example, a prevalence of fewer than 1 in 50,000 individuals has been a criterion used to define ultra-rare in literature[1] and by the NIH[2]. Yet, others have defined ultra-rare more stringently by reserving the term for only those disorders impacting fewer than 30 individuals across the world[3].

While the majority of such conditions present during childhood, several adult-onset disorders meet criteria for being labeled as orphan or rare. The etiology and age of presentation of these diseases may vary widely, but what they have in common is their rarity. The report from National Commission on Orphan Diseases in 1989 noted that 15% of the patients with rare diseases went *without a diagnosis for more than 6 years.* Further, patients and families had significant challenges in finding pertinent information sources after the diagnoses were made; approximately 74% of them were not able to identify new treatment advances and 68% had limited access to support groups.

Orphan diseases are often synonymous with genetic disorders; however, they can also include other conditions such as autoimmune, infectious, environmental, or cancers based on prevalence. Although ultra-rare diseases can have many etiologies, this response will focus on those that have a genetic basis, caused by a variant(s) in a single gene, with a specific and or unique phenotype where the gene-disease association as well as the mechanism by which the gene causes the disease have been well established.

When developing definitions of ultra-rare genetic disorders that have implications for access to cell and gene therapies, multiple factors must be considered. Traditionally, the naming of ultra-rare genetic disorders is complex and may reflect common manifestations of the diagnosis or the names of the individuals who initially discovered the disorder rather than the specific genetic basis of the diagnosis[4,5]. For instance, in some cases, the same ultra-rare genetic disorder may be caused by a

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[1] Smith CIE, Bergman P, Hagey DW. Estimating the number of diseases - the concept of rare, ultra-rare, and hyper-rare. iScience. 2022 Jul 1;25(8):104698. doi: 10.1016/j.isci.2022.104698. PMID: 35856030; PMCID: PMC9287598.

[2] https://grants.nih.gov/grants/guide/pa-files/PAR-22-028.html

[3] Crooke ST. A call to arms against ultra-rare diseases. Nat Biotechnol. 2021 Jun;39(6):671-677. doi: 10.1038/s41587-021-00945-0. PMID: 34089038.

[4] Biesecker LG, Adam MP, Alkuraya FS, Amemiya AR, Bamshad MJ, Beck AE, Bennett JT, Bird LM, Carey JC, Chung B, Clark RD, Cox TC, Curry C, Dinulos MBP, Dobyns WB, Giampietro PF, Girisha KM, Glass IA, Graham JM Jr, Gripp KW, Haldeman-Englert CR, Hall BD, Innes AM, Kalish JM, Keppler-Noreuil KM, Kosaki K, Kozel BA, Mirzaa GM, Mulvihill JJ, Nowaczyk MJM, Pagon RA, Retterer K, Rope AF, Sanchez-Lara PA, Seaver LH, Shieh JT, Slavotinek AM, Sobering AK, Stevens CA, Stevenson DA, Tan TY, Tan WH, Tsai AC, Weaver DD, Williams MS, Zackai E, Zarate YA. A dyadic approach to the delineation of diagnostic entities in clinical genomics. Am J Hum Genet. 2021 Jan 7;108(1):8-15. doi: 10.1016/j.ajhg.2020.11.013. PMID: 33417889; PMCID: PMC7820621.

[5] Hamosh A, Amberger JS, Bocchini CA, Bodurtha J, Bult CJ, Chute CG, Cutting GR, Dietz HC, Firth HV, Gibbs RA, Grody WW, Haendel MA, Lupski JR, Posey JE, Robinson PN, Schriml LM, Scott AF, Sobreira NL, Valle D, Wu N,

pathogenic variant(s) in multiple different genes. In other cases, different variants in the same gene may cause very distinct diagnoses. Thus, the causative gene and, in some cases, specific variant(s) in that gene should be considered when defining a specific ultra-rare genetic disorder.

The nuances in defining ultra-rare genetic disorders have implications for cell and gene therapies. For instance, some cell and gene therapy products may target only one of the genes associated with a given diagnosis. Alternatively, some cell and gene therapy products may be developed to target only a specific variant in a single gene. As a result, some cell and gene therapy products may be efficacious in only a small subset of individuals with the same ultra-rare genetic diagnosis. These complexities highlight the need for medical geneticists and genetic counselors in the precise diagnosis of individuals with ultra-rare genetic disorders and demonstrate the important role of medical geneticists in the decision-making processes regarding the potential utility of a specific therapy for a particular individual with an ultra-rare genetic disorder. Likewise, these caveats highlight the critical role of medical geneticists in clinical trials involving cell and gene therapy products as an understanding of these nuances is essential for enrolling appropriate patients and interpreting the results of these trials[6].

Types of treatments:

Historically, management of ultra-rare genetic disorders has primarily involved the treatment of symptoms or complications. For instance, a patient who had seizures secondary to their genetic diagnosis was managed with anti-seizure medication. Alternatively, a patient who had developmental delay as a part of their diagnosis received physical and speech therapy. There was no 'cure' or 'disease-modifying therapy' until recently. However, over the last couple of decades, fueled by basic science research and evolution of molecular genetics, several precision therapies have been approved and/or are in trial that work by targeting the underlying genetic defect in some way. These therapies include cell and gene therapy.

Per the American Society of Gene & Cell Therapy (ASGCT), gene therapy is the use of genetic material in the treatment or prevention of disease. The transferred genetic material changes how a single protein or group of proteins is produced by the cell. Gene therapy can be used to reduce levels of a disease-causing version of a protein, to increase production of disease-fighting proteins, or to produce new/modified proteins. In May 2019, the FDA approved Zolgensma to treat spinal muscular atrophy in children under two years old. In June 2023, U.S. Food and Drug Administration approved Elevidys, the first gene therapy for the treatment of pediatric patients 4 through 5 years of age with Duchenne muscular dystrophy (DMD) with a confirmed pathogenic variant in the DMD gene. There are different types of gene therapy. Gene addition involves inserting a new copy of a gene into the target cells to produce more of a protein. Gene correction, gene silencing, and reprogramming are other mechanisms that also fall under the category of gene therapy.

Rasmussen SA. Response to Biesecker et al. Am J Hum Genet. 2021 Sep 2;108(9):1807-1808. doi: 10.1016/j.ajhg.2021.07.004. PMID: 34478655; PMCID: PMC8456153.

[6] Peña LDM, Burrage LC, Enns GM, Esplin ED, Harding C, Mendell JR, Niu ZN, Scharfe C, Yu T, Koeberl DD; ACMG Therapeutics Committee. Electronic address: documents@acmg.net. Contributions from medical geneticists in clinical trials of genetic therapies: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023 Jun;25(6):100831. doi: 10.1016/j.gim.2023.100831. Epub 2023 Apr 9. PMID: 37031408.

In contrast, the ASGCT defines cell therapy as the transfer of intact, live cells into a patient to help lessen or cure a disease. The cells may originate from the patient (autologous cells) or a donor (allogeneic cells). The type of cells administered depends on the treatment. For example, CAR T-cell therapies have been approved by the FDA to treat aggressive B-cell lymphomas in adults (Yescarta and Kymriah) and B-cell leukemia in children and young adults (Kymriah). Hematopoietic stem cell transplantation (HSCT) is a type of cell therapy used to improve survival in patients with cerebral adrenoleukodystrophy, a rapidly progressive neurogenetic condition.

Although the focus of this response is gene and cell therapies, other types of genetic therapies may be important for consideration in the treatment of ultra-rare diseases, such as anti-sense oligonucleotides (ASOs), which are short, synthetic, single-stranded oligodeoxynucleotides that can alter RNA and reduce, restore, or modify protein expression through several distinct mechanisms. For example, the FDA approved nusinersen, an ASO therapy, in December 2016 to treat spinal muscular atrophy (SMA) associated with an *SMN1* gene mutation. It is administered directly to the central nervous system by intrathecal injection. ASO therapies inhibit gene expression by binding to messenger RNA (mRNA), causing them to be cut into pieces that interfere with the creation of coded proteins. Other types of therapies, such as other RNA therapies, small molecule drugs, and enzyme-replacement therapies, may be important in treating ultra-rare diseases. Like gene and cell therapies, some of these therapies can be costly, require travel to specialty sites for administration, or have other factors that impact patient access.

RFI Section: How Do Physicians Provide Access to These Therapies?

34. *How does a physician or health system initiate the process of prescribing a patient with an ultra-rare disease or disorder one of these therapies?*
35. *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?*
36. *What is the typical communication between the physician, health system, and manufacturer as a part of prescribing a patient with an ultra-rare disease or disorder these therapies?*
37. *What is the typical communication between the physician, health system, and health plan or payer as part of prescribing a patient with an ultra-rare disease or disorder these therapies?*
38. *Do physicians or patients with an ultra-rare disease or disorder use a dispensing channel similar to other physician-administered treatments to access these therapies, or is there an alternative method?*

Physician considerations in providing access:

As stated by Vockley et al.[7], despite the recent increase in investigational new drug applications for gene therapies, the fact that there are over 7,000 rare disorders would make it impossible for all disorders to have a specific gene therapy within the next few decades. However, the push by various groups from different backgrounds (medical, patients/families, industry) has slowly and steadily changed this situation.

[7] Vockley J, Defay T, Goldenberg AJ, Gaviglio AM. Scaling genetic resources: New paradigms for diagnosis and treatment of rare genetic disease. Am J Med Genet C Semin Med Genet. n/a(n/a). doi:10.1002/ajmg.c.32016

Taking examples from approved biological therapies, such as pegvaliase-pqpz, most if not all therapies (including gene therapies) require extensive labor by both prescribing physicians, medical institutions, industry, and payors. Gene and other biological therapies, in particular, require an extensive process that starts with individual and family counseling by experienced healthcare professionals (HCPs) on how these therapies could change the clinical status of the affected individual as well as conveying that, given the relative novelty, the long-term effects are still unknown as there is no extended data. Following this understanding, all individuals undergo specific clinical evaluations to determine their eligibility according to the approved therapy protocol and mechanism of action[8,9,10,11]. To some extent, these visits are covered by a payor (medical insurance, family out-of-pocket costs, or public).

When eligibility is appropriate, HCPs obtain prior insurance authorizations or request sponsor (industry) coverage according to different variables, such as novelty of therapy or insurance requirements. Like any other, this process could take weeks or months due to the extensive information required for a payor to provide coverage.

Following payor approval, healthcare institutions would follow specific institutional and therapy protocol guidance towards administering said therapy. As the delivery methods, mechanisms of actions, monitoring, and surveillance could vary among therapies, multiple institutional resources would be allocated, including personnel (pharmacy, medical assistants, registered nurses, nurse practitioners, physician assistants, physicians) towards the single administration of these therapies. Therefore, some expenses not covered by the original payor would have to be absorbed by the healthcare institution or transferred to the affected individual and their family.

Understandably, not all centers across the United States would have the capacity to provide said therapies due to the need for experienced physicians and high-quality assets. In addition to the centers/institutions that have developed these therapies through clinical trials, other specialized centers, such as the National Organization for Rare Disorders Centers of Excellence[12], should be primarily considered to provide these therapies, given their expertise in this area.

There is certainly a financial risk with these new treatment modalities. These novel therapies and new mechanisms of action are just starting to become widely accepted by the medical community as viable treatment options. Because these are new technologies, the up-front cost to the health system is significant. The institution may assume this risk as part of a “buy-and-bill” arrangement, where the hospital purchases the treatment and then bills insurance for its cost. With regard to mitigating the

[8] Stoner N. Are UK hospital pharmacy departments ready for the rise of gene therapy medicinal products? Expert Opin Biol Ther. 2018;18(8):837-840. doi:10.1080/14712598.2018.1495192
[9] Petrich J, Marchese D, Jenkins C, Storey M, Blind J. Gene Replacement Therapy: A Primer for the Health-system Pharmacist. doi:10.1177/0897190019854962
[10] Pena, L. D. M., Burrage, L. C., Enns, G. M., Esplin, E. D., Harding, C., Mendell, J. R., Niu, Z. N., Scharfe, C., Yu, T., Koeberl, D. D. et al. (2023). Contributions from medical geneticists in clinical trials of genetic therapies: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 100831.
[11] Lenahan, A. L., Squire, A. E., and Miller, D. E. (2023). Panels, exomes, genomes, and more—finding the best path through the diagnostic odyssey. Pediatr. Clin. N. Am. 70, 905–916. doi:10.1016/j.pcl.2023.06.001
[12] https://rarediseases.org/center-of-excellence/

high costs of gene therapy, long-term data does not exist (currently) to determine the endurance of these therapies. However, the power of the potential benefits from these therapies can mean significant long-term gains and improvements in health outcomes, which can reduce the overall burden on the healthcare system for each individual treated.

Access to these therapies will also encompass increased HCP training through various methods and sources such as the Therapeutic Bulletins from the ACMG[13,14], a concise revision of what is known about the newly approved therapy (to date of publication); systematic evidence reviews and evidence-based guidelines, such as those published by the ACMG; or concise reviews by interested clinical research groups (e.g., international working groups with specific interests like neurotransmitter disorders).

RFI Section: What is the Future of Access for These Therapies?

39. *What is the appropriate role of the federal government in ensuring access to these therapies in the commercial market? How can any steps taken on the federal level ensure expanded access while not hurting innovation in this area?*
49. *Should health care providers share in the financial risk of prescribing these therapies to patients? Why or why not?*
52. *How should policymakers consider other eligibility criteria for access to these therapies for populations such as individuals with long-term disabilities or complex medical needs who are eligible for Medicaid based on disability? What role should commercial insurance play in the long-term for covering these patients who may no longer have the disability that made them Medicaid eligible?*

Ensuring access and supporting innovation:

Currently, a majority of gene and other related biological therapies are promoted by private investors who have seen a need to aid affected individuals and their families. However, this profit-driven model is subject to market volatility and the possibility of premature closure of clinical trials. While some of these trials could be transferred/sold to another private company for continuation[15], not all trial therapies undergo the same route, and some fall into oblivion. ,While the sponsor/company bears much risk in bringing these therapies to trial, at the moment, the only oversight for the research is from the FDA and Department of Health and Human Services (HHS) to monitor risk for human subjects and potential efficacy. When a program closes at the trial stage, valuable data regarding the mechanism of action, preliminary efficacy, and safety are lost, and patients lose access to a drug that could directly benefit their health. Therefore, the federal government should consider strong support

[13] Arthur Lenahan, Sho Yano, Brett Graham, Kuntal Sen, on behalf of the ACMG Therapeutics Committee (2023). Omaveloxolone approved for patients aged 16 years and older with Friedreich ataxia (FRDA): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG). *Genet Med Open*. DOI: https://doi.org/10.1016/j.gimo.2023.100832

[14] Anna I. Scott, Kanwaldeep K. Mallhi, Jaya Ganesh, Wei-Liang Chen, on behalf of the ACMG Therapeutics Committee (2023). Elivaldogene autotemcel approved for treatment of cerebral adrenoleukodystrophy (CALD) in males: A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG). *Genet Med Open*. DOI: https://doi.org/10.1016/j.gimo.2023.100835

[15] https://www.prnewswire.com/news-releases/aeglea-biotherapeutics-announces-sale-of-pegzilarginase-to-immedica-pharma-301887231.html

in all steps of therapy development and approval to avoid serious complications at the individual and societal levels.

Following therapy approval, the federal government could be a strong player in guiding coverage. As outlined above, healthcare institutions and affected individuals/families will absorb some of the cost of these therapies due to different factors like reduced productivity (individual/family) leading to reduced income, costs not covered by insurance but required for the proper administration of therapies (like specialized staff such as pharmacists, registered nurses, physicians), or subsequent surveillance (including multiple subspecialty visits, caregiver time, monitoring labs)[16,17,18].

Although these initial costs could be considered extraordinary at first, a treated individual with a successful response would significantly reduce lifetime healthcare expenses as there would be fewer hospitalizations due to acute clinical decompensations and decreased need for specialized multidisciplinary care. Furthermore, societal productivity, from a single treated individual, would significantly impact the workforce[19]. However, further data is needed to specifically quantify the future impact of these therapies due to the need for more available prospective data (given the relative novelty).

Therapy financing should be a conjoined effort by the federal government (public) and industry (private) as neither could take the cost burden nor navigate the intricacies of development and administration, alone. Each would have a specific role to fill. For example, private companies could develop therapy proof of concept with academic researchers from various backgrounds. Researchers would then have an easy way of identifying suitable individuals for these therapies and, with the support of public-private financing, start therapeutic trials to assess beneficence and effectiveness. The federal government could provide a regulatory framework for therapy approval and distribution, and supply extra funding for individuals from disadvantaged backgrounds. An early and possibly successful federal government involvement is the Bespoke Gene Therapy Consortium, an NIH-related initiative aiming to provide models for developing diagnostics and therapies as conjoined government, academic and industry alliance[20].

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[16] James D. Chambers P, Ari D. Panzer BS, David D. Kim P, Nikoletta M. Margaretos BA, Peter J. Neumann S. Variation in US Private Health Plans' Coverage of Orphan Drugs. 2019;25. Accessed May 25, 2023. https://www.ajmc.com/view/variation-in-us-private-health-plans-coverage-of-orphan-drugs

[17] Handfield R, Feldstein J. Insurance Companies' Perspectives on the Orphan Drug Pipeline. Am Health Drug Benefits. 2013;6(9):589-598.

[18] Danzon PM. Affordability Challenges to Value-Based Pricing: Mass Diseases, Orphan Diseases, and Cures. Value Health. 2018;21(3):252-257. doi:10.1016/j.jval.2017.12.018

[19] Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007;23(1):36-42. doi:10.1017/S0266462307051550

[20] https://ncats.nih.gov/research/research-activities/BGTC#:~:text=NIH%2C%20FDA%20and%2015%20Private,Gene%20Therapies%20for%20Rare%20Diseases&text=NIH%2C%20FDA%20and%2015%20private%20organizations%20partnered%20to%20create%20the,NCATS%20and%20managed%20by%20FNIH

Physician share of financial risk:

HCPs should be able to provide healthcare within their scope of practice and training without fear of unnecessary financial risks. Placing a share of the financial risk on HCPs would create an additional burden that may deter physicians from entering the rare disease field, which is already facing significant workforce shortages. This is consistent with the fact that physicians do not benefit from prescribing these therapies.

Commercial and government insurance:

Eligibility for treatment should be independent of dependence on private or government-funded insurance. Some of these therapies are best implemented early in life, on occasion within six weeks of a diagnosis (e.g., see the data for a profound benefit in infants diagnosed with type 1 SMA). This impacts federally funded programs with an annual budget set in advance and commercial payors who cannot act within the short timeframe necessary for the therapy to be effective. Hence, there may be inherent disadvantages to access for patients with either insurance type.

Additional Considerations:

The following points should be considered when evaluating policy needs to support access to therapies for ultra-rare diseases.

- All individuals should have access to a precise genetic diagnosis that will enable them to qualify for such therapies (a precise genetic diagnosis is typically required for eligibility). This includes equal access to trained genetic health professionals and genetic diagnosis services, including genetic testing. Careful consideration must be given to the potential impact of policies for regulating genetic testing on the availability of and access to tests for rare and ultra-rare diseases.
- All individuals should have access to such therapies regardless of race, sex, geographic location, and socioeconomic status if they have a precise genetic diagnosis that qualifies them for the therapy. All individuals should have access to such therapies regardless of age if the therapy is demonstrated to have efficacy across all age groups.
- The efficacy of cell and gene therapy for a particular ultra-rare genetic disorder should be supported by strong evidence to be covered. Given the small number of available patients for traditional clinical trials, this efficacy can be challenging to demonstrate in the setting of ultra-rare diagnoses. Thus, there should be support to establish an infrastructure (e.g., large collaborative nationwide networks) that supports data-sharing regarding the natural history of the disorder and identification of candidate patients for therapy trials to allow for efficient and rigorous validation of new therapies. Such networks are also critical for long-term follow-up of patients with these disorders as newer therapies may introduce new complications that were previously unrecognized and/or side effects that were not previously reported.
- Although some therapies may be curative, others may only mitigate some aspects of the diagnosis. Thus, coverage of such therapies should not prevent patients from accessing other needed services for long-term follow-up, including other therapies.
- As therapies become available, an infrastructure that incentivizes seeking treatment may be beneficial to reduce the overall burden of healthcare costs associated with the diagnosis.

ACMG appreciates the opportunity to provide feedback on this request for information. For questions or follow-up discussion, please contact Michelle McClure, PhD, ACMG Director of Public Policy at mmcclure@acmg.net.

Sincerely,

Susan D. Klugman, MD, FACMG
President
American College of Medical Genetics and Genomics