

Rare Diseases and the New Era of Diagnosis and Treatment

Sri Aditya Domakuntla, Umesh Ummalaneni, and Saharsh Chalumalla
dsriaditya22@gmail.com, umeshummalaneni@gmail.com, saharshc06@gmail.com

ABSTRACT

Rare diseases are individually uncommon but collectively affect hundreds of millions of people. This narrative review examines how rare diseases are defined, why diagnosis is frequently delayed, how orphan-drug policy has changed treatment development, and how genomic sequencing, artificial intelligence, gene therapy, and gene editing are reshaping care. The literature was identified through targeted searches of biomedical databases and authoritative government, clinical, and patient-advocacy sources, with emphasis on publications from 2015 through June 2026. Evidence indicates that patients often experience years of diagnostic delay and that only a small share of known rare diseases has an approved treatment. Recent advances, including personalized in vivo gene editing, demonstrate the possibility of therapies designed for extremely small patient populations. However, most personalized and gene-editing approaches remain experimental, require specialized infrastructure, and have limited long-term safety and effectiveness data. Progress is also distributed unevenly: access to newborn screening, genomic testing, specialists, and orphan drugs is substantially greater in well-resourced health systems. Scientific innovation therefore must be paired with stronger referral networks, diverse genomic data, sustainable financing, international collaboration, and patient-centered policy.

Keywords: rare diseases, orphan drugs, diagnostic odyssey, genomic sequencing, gene therapy, CRISPR, newborn screening

INTRODUCTION

Clinicians are often taught that when they hear hoofbeats, they should think of horses rather than zebras. The saying encourages attention to common diagnoses before unusual ones. For people living with a rare disease, however, the zebra is the correct answer. Symptoms may resemble more common conditions, few clinicians may have encountered the disease, and appropriate testing may not be readily available. The zebra has consequently become a symbol of the rare disease community and a reminder that disorders that are uncommon individually are impossible to ignore collectively.

A disease is categorized as rare according to prevalence rather than severity or biological mechanism. In the United States, a disease generally qualifies as rare when it affects fewer than 200,000 people; the European Union uses a threshold of no more than 1 in 2,000 people [3]. Researchers have described

approximately 7,000 to 10,000 rare diseases, and new conditions continue to be identified as genomic and computational tools improve [2,4]. Taken together, rare diseases affect an estimated 300 million people worldwide [1]. Approximately 72 percent are genetic and about 70 percent begin during childhood [1]. Many are progressive, life-limiting, or disabling, yet most still lack a disease-specific treatment.

This review summarizes the epidemiology and economic burden of rare diseases, the causes and consequences of diagnostic delay, policy incentives for treatment development, emerging genomic and gene-editing therapies, patient advocacy, and persistent global inequities. Particular attention is given to the need for a balanced interpretation of emerging therapies: recent breakthroughs are scientifically important, but early individual successes do not yet establish broad clinical effectiveness.

REVIEW METHODOLOGY

This article is a narrative review. The literature base was assembled through targeted searches conducted between May and July 2026 using PubMed, Google Scholar, Orphanet, and the websites of the U.S. Food and Drug Administration, National Institutes of Health, U.S. Government Accountability Office, EURORDIS-Rare Diseases Europe, and Rare Diseases International. Search terms included combinations of "rare disease," "orphan drug," "diagnostic delay," "genomic sequencing," "artificial intelligence," "gene therapy," "CRISPR," "personalized therapy," "newborn screening," and "global access."

English-language sources published from 2015 through June 2026 were emphasized, while older foundational policy sources and landmark studies were retained when necessary. Sources were included when they provided population-level prevalence or cost estimates, multinational patient survey data, regulatory or policy information, clinical evidence on approved or investigational therapies, or information from established patient-advocacy organizations. Peer-reviewed studies and government or intergovernmental reports were prioritized over commentary. Because this was not a systematic review, the search was not designed to capture every eligible publication, and no formal risk-of-bias assessment or meta-analysis was performed.

DEFINING RARE DISEASES

No single prevalence threshold is used worldwide. The United States definition is rooted in the Orphan Drug Act of 1983, whereas the European Union uses a population-based threshold [3]. Some conditions described as ultra-rare affect fewer than 1 in 50,000 people, and certain genetic disorders have been documented in only a few families. Definitions also differ in whether they include rare cancers, infections, congenital conditions, and subtypes of more common diseases. These differences complicate international comparisons, regulatory decisions, and estimates of the total number of affected patients.

Most rare diseases result from a pathogenic change in one gene, although chromosome abnormalities, multifactorial mechanisms, immune dysfunction, cancers, and infections also contribute. A genetic cause often makes DNA analysis central to diagnosis and creates a potential molecular target for treatment. At the same time, rare variants can be difficult to interpret, especially when reference databases do not

adequately represent the patient's ancestry. A laboratory result is therefore most useful when combined with careful clinical evaluation, family history, and appropriate counseling.

PREVALENCE AND ECONOMIC BURDEN

An analysis of the Orphanet database estimated that 3.5 to 5.9 percent of the global population lives with a rare disease at a given time, corresponding to roughly 300 million people [1]. This estimate is likely conservative because many diseases are missing from registries or health records, and the analysis excluded some rare cancers and infectious diseases [1,4]. The burden is also highly uneven: a limited number of better-known diseases account for many patients, while thousands of ultra-rare conditions affect very small and geographically dispersed groups. This distribution makes conventional clinical trials, natural history studies, and commercial drug development more difficult.

Rare diseases also create major direct and indirect costs. A U.S. study examining 379 rare diseases estimated a total economic burden of approximately \$966 billion in 2019, including \$418 billion in direct medical costs and \$548 billion in productivity loss, unpaid caregiving, and other nonmedical costs [7]. Because the analysis covered only a fraction of known rare diseases, the full burden is likely greater. Families may also face travel to distant specialty centers, repeated testing, reduced work hours, school disruption, and the emotional cost of prolonged uncertainty.

THE DIAGNOSTIC ODYSSEY

The prolonged search from the first symptom to a confirmed diagnosis is commonly called the diagnostic odyssey. Delay occurs because symptoms overlap with common disorders, clinicians may have limited rare disease experience, phenotypes can change with age, and access to specialists and genomic testing varies. The consequences extend beyond frustration: patients may receive ineffective or harmful treatments, miss time-sensitive interventions, and experience avoidable disease progression and psychological stress.

A EURORDIS Rare Barometer survey included 6,507 people living with 1,675 rare diseases in 41 European countries. Participants reported an average diagnostic delay of 4.7 years; women waited an average of 5.4 years compared with 3.7 years for men, and patients whose symptoms began between ages 10 and 19 experienced especially long delays [6]. Approximately six in ten respondents had initially received an incorrect diagnosis, and many consulted at least four clinicians before receiving an answer [6,15]. Earlier referral to an expert center was associated with shorter delays, supporting stronger referral pathways and wider access to multidisciplinary rare disease clinics.

Genomic sequencing has improved the ability to investigate unexplained disease. Multigene panels, exome sequencing, and genome sequencing can evaluate thousands of genes simultaneously, while rapid sequencing can produce clinically useful results for critically ill infants within days. Reanalysis is also important: a variant that is uninterpretable today may become diagnostic after new disease-gene relationships are discovered. However, sequencing does not guarantee an answer. Some causal variants

remain technically hard to detect, disease mechanisms may not be genetic, and uncertain findings require careful interpretation.

Artificial intelligence can assist with phenotype recognition and diagnostic prioritization. Deep-learning systems that analyze facial features have ranked the correct syndrome among their leading suggestions in many test cases, and related tools can organize clinical features or search medical records for patterns [8,9]. These systems should support rather than replace clinicians. Performance may decline in populations that were poorly represented during training, and the use of facial images, genomic data, and health records raises concerns about privacy, consent, explainability, and unequal error rates.

WHY SO FEW TREATMENTS EXIST

Before the Orphan Drug Act, small patient populations gave manufacturers little financial incentive to develop rare disease therapies. The 1983 law introduced benefits such as market exclusivity, tax incentives, research grants, and regulatory support. Similar policies were later adopted in Europe and other regions. During the first 40 years of the U.S. law, orphan designations covered more than 1,000 rare diseases and contributed to approved treatments for 392 of them [5]. Rare disease products now represent a substantial share of newly approved medicines [4].

Despite this progress, only about 5 percent of known rare diseases have an approved treatment [4,5]. Drug development remains challenging because patient populations are small, geographically dispersed, and often clinically diverse. Researchers may lack reliable natural history data or validated outcome measures, and randomized trials may be impractical. Regulators and investigators therefore use adaptive designs, external control groups, biomarkers, patient registries, and real-world evidence when scientifically appropriate. These approaches can make development more feasible but do not eliminate the need for rigorous evidence.

Cost is another major barrier. Some gene and enzyme-replacement therapies cost hundreds of thousands or millions of dollars per patient and may require specialized hospitals, long-term monitoring, or repeated treatment. High prices can restrict insurance coverage and strain public health budgets. Incentives that successfully stimulate innovation must therefore be paired with transparent evidence standards, sustainable payment models, and policies that prevent the existence of a therapy from becoming disconnected from patients' ability to obtain it.

EMERGING TREATMENTS AND GENE EDITING

Rare disease treatment now includes enzyme replacement, small molecules, antisense oligonucleotides, RNA therapies, gene addition, stem-cell-based approaches, and genome editing. Luxturna, approved in 2017, uses gene augmentation for inherited retinal disease, and Zolgensma, approved in 2019, delivers a functional gene for spinal muscular atrophy. Gene therapies have also been approved for hemophilia, beta thalassemia, Duchenne muscular dystrophy, and other conditions. In 2023, the FDA approved Casgevy for sickle cell disease, the first approved therapy to use CRISPR-based genome editing [11].

Personalized treatment extends precision medicine to variants found in only one patient or a very small group. In 2019, investigators reported a customized antisense oligonucleotide developed for a child with a unique form of neuronal ceroid lipofuscinosis [10]. In 2025, a team at Children's Hospital of Philadelphia and the University of Pennsylvania reported a patient-specific in vivo base-editing therapy for an infant with severe carbamoyl phosphate synthetase 1 deficiency. The therapy was designed around the patient's specific variant, delivered to the liver using lipid nanoparticles, and administered through a single-patient expanded-access pathway [12-14]. Early follow-up showed improved metabolic control and reduced medication requirements without a reported serious treatment-related adverse event [12].

The case is an important proof of concept, not evidence that individualized gene editing is ready for routine use. It involved one patient, follow-up was short, and the treatment required an unusually large network of academic, industry, regulatory, and manufacturing partners. Questions remain about off-target editing, immune responses, durability, repeat dosing, informed consent, long-term monitoring, manufacturing quality, and cost. Many gene-editing strategies are still in preclinical or early clinical development, and methods that work for liver-targeted disorders may not translate easily to the brain, muscle, lung, or other tissues. Wider use will require reusable platforms, standardized regulatory pathways, transparent safety surveillance, and evidence from more patients.

Artificial intelligence may accelerate therapeutic discovery by matching existing drugs to new indications, predicting molecular interactions, prioritizing variants, and helping design candidate molecules. These tools may be especially useful when a disease population is too small to support a conventional discovery program. Their predictions still require laboratory and clinical validation, and proprietary models or nonrepresentative training data can introduce new barriers rather than remove existing ones.

PATIENT ADVOCACY AND PUBLIC HEALTH

Patients and families have shaped rare disease policy, research funding, registries, trial recruitment, and public awareness. Organizations such as the National Organization for Rare Disorders, EURORDIS-Rare Diseases Europe, and disease-specific foundations connect families with clinicians and researchers, support natural history studies, and advocate for regulatory change [15,16]. Rare Disease Day, observed on the last day of February, has developed into a global awareness campaign [16]. For ultra-rare conditions, a family-led foundation may provide the first organized funding and patient network available to scientists.

Registries and expert networks are especially important because no single institution may see enough patients to characterize a disease. Shared data can improve diagnosis, identify trial participants, and reveal how a condition changes over time. Data sharing must be accompanied by meaningful consent, privacy protection, interoperable standards, and governance that includes patients and the communities contributing the data.

Newborn Screening

Newborn screening can prevent a diagnostic odyssey when a serious condition is detectable before symptoms and effective early treatment is available. Screening programs typically begin with dried blood spots and may also include hearing or cardiac testing. As therapies develop, additional rare conditions become candidates for screening. Expansion requires evidence that the test is accurate, confirmatory services are available, treatment can begin promptly, and benefits outweigh the risks of false-positive or uncertain results. The possible addition of broad genomic sequencing raises further questions about parental consent, findings that predict adult-onset disease, data storage, and whether it is appropriate to report conditions for which no effective intervention exists.

A GLOBAL ACCESS GAP

The benefits of rare disease innovation are distributed unevenly. High-income health systems are more likely to have national or regional newborn screening panels, clinical genetics services, sequencing laboratories, specialty centers, regulatory incentives, and insurance or public reimbursement for orphan drugs. Even among wealthy countries, screening panels and covered therapies differ. In many low-resource settings, newborn screening may be limited to a small number of conditions, laboratory capacity may be concentrated in major cities, and confirmatory testing or samples may need to be sent abroad [17]. These delays can eliminate the benefit of treatments that must begin before irreversible injury occurs.

The falling price of DNA sequencing has not removed the infrastructure gap. Genomic diagnosis also requires trained clinicians, genetic counselors, bioinformaticians, reliable sample transport, computing resources, and reference databases that represent local populations. Genomic studies have historically overrepresented people of European ancestry, which can increase uncertain results and reduce diagnostic accuracy for other groups [18]. Sustainable progress therefore depends on local laboratory and workforce development, equitable international partnerships, and governance that allows communities to share in the benefits produced from their data.

Orphan-drug availability also varies across regulatory and payment systems. A medicine approved in the United States or European Union may not be registered, reimbursed, or supplied in another country. Reviews of national orphan-drug policies show substantial differences in incentives, approval pathways, pricing, and coverage [19]. For advanced therapies, access additionally depends on cold-chain logistics, specialized hospital facilities, and long-term follow-up. Without tiered pricing, pooled procurement, regional treatment centers, public financing, and technology transfer, scientific breakthroughs may widen rather than reduce global inequity.

CHALLENGES AHEAD

The central challenge is no longer whether rare diseases can be diagnosed and treated more effectively, but how scientific advances can become dependable and equitable care. Faster diagnosis will require

clinician education, clear referral pathways, broader access to sequencing, periodic reanalysis, and responsible use of artificial intelligence. Treatment development will require international natural history studies, shared outcome measures, flexible but rigorous trials, and policies that make high-cost therapies sustainable.

Personalized therapies create additional ethical and regulatory questions. Decisions must account for the uncertainty of first-in-human treatment, the limited alternatives available to severely ill patients, and the difficulty of obtaining long-term evidence from one-person interventions. Regulators will need approaches that evaluate reusable platforms efficiently without treating every variant as an entirely unrelated product. Patients and families should be partners in designing consent, follow-up, data sharing, and access policies.

Finally, progress depends on sustained basic research. Many rare diseases still lack a known molecular cause, a validated model, or a measurable biomarker. Investment in foundational biology may not produce an immediate therapy, but it creates the knowledge on which sequencing interpretation, drug discovery, and gene editing depend. The goals of shortening diagnosis from years to months and increasing the proportion of treatable rare diseases are ambitious, but recent advances show that they are scientifically achievable.

CONCLUSION

Rare diseases reveal a public health paradox: each condition affects relatively few people, yet together they affect hundreds of millions. Genomic sequencing, artificial intelligence, orphan-drug policy, gene therapy, and gene editing have changed what is possible, including the development of a treatment for a single patient. These advances should be interpreted with both optimism and caution. Most rare diseases still lack an approved therapy, personalized editing remains experimental, and access to diagnosis and treatment is deeply unequal. The next era of rare disease care must therefore combine scientific innovation with transparent evidence, long-term safety monitoring, affordable access, diverse genomic data, international capacity building, and continued leadership from patients and families. No patient population is too small to deserve rigorous research and effective care.

ACKNOWLEDGMENTS

The authors thank their teachers and families for supporting their interest in rare disease research and patient advocacy. The authors also recognize the patients and families whose participation in research and public advocacy makes progress in this field possible.

REFERENCES

1. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet.* 2020;28(2):165-173.
2. Haendel M, Vasilevsky N, Unni D, Bologna C, Harris N, Rehm H, et al. How many rare diseases are there? *Nat Rev Drug Discov.* 2020;19(2):77-78.
3. U.S. Food and Drug Administration. Rare Diseases at FDA. Silver Spring, MD: FDA; 2024. Available from: <https://www.fda.gov/patients/rare-diseases-fda>
4. U.S. Government Accountability Office. Rare Disease Drugs: FDA Has Steps Underway to Strengthen Coordination of Activities Supporting Drug Development. Report GAO-25-106774. Washington, DC: GAO; 2025.
5. Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. *Orphanet J Rare Dis.* 2023;18(1):163.
6. Dubief J, Faye F; EURORDIS Rare Barometer Programme. Time to diagnosis and determinants of diagnostic delays of people living with a rare disease: results of a Rare Barometer retrospective patient survey. *Eur J Hum Genet.* 2024. doi:10.1038/s41431-024-01604-z.
7. Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. *Orphanet J Rare Dis.* 2022;17(1):163.
8. Gurovich Y, Hanani Y, Bar O, Nadav G, Fleischer N, Gelbman D, et al. Identifying facial phenotypes of genetic disorders using deep learning. *Nat Med.* 2019;25(1):60-64.
9. Rudy NL, Gomes A, Bird LM, et al. Artificial intelligence software changes rare disease testing strategy in real time: an international case series using Face2Gene. *Am J Med Genet A.* 2025. doi:10.1002/ajmg.a.64171.
10. Kim J, Hu C, Moufawad El Achkar C, Black LE, Douville J, Larson A, et al. Patient-customized oligonucleotide therapy for a rare genetic disease. *N Engl J Med.* 2019;381(17):1644-1652.
11. U.S. Food and Drug Administration. FDA approves first gene therapies to treat patients with sickle cell disease [news release]. Silver Spring, MD: FDA; December 8, 2023.
12. Musunuru K, Grandinette SA, Wang X, Hudson TR, Briseno K, Berry AM, et al. Patient-specific in vivo gene editing to treat a rare genetic disease. *N Engl J Med.* 2025;392(22):2235-2243.
13. Children's Hospital of Philadelphia. World's first patient treated with personalized CRISPR gene editing therapy at Children's Hospital of Philadelphia [news release]. Philadelphia, PA: CHOP; 2025. Available from: <https://www.chop.edu>
14. National Institutes of Health. Infant with rare, incurable disease is first to successfully receive personalized gene therapy treatment [news release]. Bethesda, MD: NIH; May 2025. Available from: <https://www.nih.gov>
15. EURORDIS-Rare Diseases Europe. Earlier, faster and more accurate diagnosis: diagnosis priorities and Rare Barometer findings. Paris: EURORDIS; 2024. Available from: <https://www.eurordis.org>

16. Rare Diseases International; EURORDIS-Rare Diseases Europe. Rare Disease Day and global advocacy for people living with a rare disease. Available from: <https://www.rarediseaseday.org>
17. Therrell BL Jr, Padilla CD, Borrajo GJC, Khneisser I, Schielen PCJL. Current status of newborn bloodspot screening worldwide 2024: a comprehensive review of recent activities (2020-2023). *Int J Neonatal Screen*. 2024;10(2).
18. Fatumo S, Chikowore T, Choudhury A, Ayub M, Martin AR, Kuchenbaecker K. A roadmap to increase diversity in genomic studies. *Nat Med*. 2022;28:243-250.
19. Gammie T, Lu CY, Babar ZU. Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries. *PLoS One*. 2015;10(10):e0140002.