

# Rare Diseases in 2025: Diagnosis, Treatment & Policy

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rare diseases

orphan drugs

genetic disorders

diagnostic odyssey

public health

drug development

gene therapy



## Executive Summary

Rare diseases are a diverse group of thousands of conditions, each affecting relatively few individuals but collectively impacting hundreds of millions worldwide. As of 2025, over 6,000 rare diseases have been identified, affecting an estimated 300–400 million people globally (around 3.5–5.9% of the population) (<sup>[1]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)) (<sup>[2]</sup> [www.weforum.org](http://www.weforum.org)). Approximately 72–80% of rare diseases have a known genetic origin, and about 70% of these conditions begin in childhood (<sup>[1]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)). Many rare diseases are severe, chronic, and life-threatening; tragically, about one in three children with a rare disease will not live beyond their 5th birthday (<sup>[3]</sup> [www.weforum.org](http://www.weforum.org)). Despite their individual rarity, rare diseases collectively pose a significant medical and public health challenge. Historically under-recognized, rare diseases are now gaining global attention as a health priority, reflected by landmark policy initiatives such as the United Nations 2021 Resolution on “Addressing the Challenges of Persons Living with a Rare Disease” and the World Health Assembly’s 2025 adoption of a resolution calling for a 10-year global action plan (<sup>[4]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)).

This report provides an in-depth examination of the rare disease landscape in 2025. It offers a comprehensive overview of the historical context, epidemiology, challenges, current state of diagnostics and therapeutics, stakeholder perspectives, case studies, economic and societal impacts, and future directions. Key findings include:

- **Prevalence and Burden:** Rare diseases affect roughly 4% of the global population – about 300 million people worldwide – with around 30 million patients in each of regions like the United States and Europe [<https://blogs.cdc.gov/genomics/2019/04/04/introducing-the-rare-diseases/>]. Each rare disease may affect only a handful to a few thousand patients, but collectively they represent a large underserved community. Rare conditions often impose devastating health impacts, including progressive disabilities and premature mortality.
- **Historical Progress:** In the last four decades, targeted legislation and incentives have spurred progress in rare diseases. The U.S. Orphan Drug Act of 1983 and similar laws in Europe (2000) and other countries catalyzed the development of [orphan drugs](#) – therapies for rare diseases. Over 1,000 orphan drugs have been approved in the U.S. as of 2024, up from virtually none before 1983 [<https://www.nome.bio/blog/orphan-drug-designation-statistics>]. Global collaborations like the International Rare Diseases Research Consortium (IRDiRC), and advocacy by patient organizations (e.g. NORD in the U.S. and EURORDIS in Europe) have further accelerated research and policy action.
- **Diagnostic Challenges:** Patients with rare diseases often face a “diagnostic odyssey.” A recent EURORDIS survey across 42 countries found an average diagnostic delay of about 4.5 years for rare disease patients, with 25% of patients waiting over 8 years for an accurate diagnosis [<https://www.nature.com/articles/s41431-024-01604-z>]. Misdiagnosis is common; many patients consult numerous doctors (often 8 or more) before getting answers (<sup>[5]</sup> [www.eurordis.org](http://www.eurordis.org)). Causes of delay include low physician awareness, atypical presentations, and limited access to specialized genetic testing. Newborn screening programs and genomic sequencing initiatives are gradually improving early detection for certain rare conditions, but timely diagnosis remains a major hurdle worldwide.
- **Therapeutic Landscape:** Only around 5% of rare diseases have an approved treatment as of 2025 ([projects.research-and-innovation.ec.europa.eu](https://projects.research-and-innovation.ec.europa.eu)). This means 95% of rare diseases lack any specific therapy, highlighting a massive unmet medical need. Nevertheless, the pace of orphan [drug development](#) has increased markedly. In recent years, over half of all new drug approvals by the FDA have been for rare disease indications [<https://www.dcatvci.org/features/orphan-drugs-still-showing-market-strength-or-not/>]. Orphan drugs now represent a significant and growing share of the pharmaceutical market (projected ~20% of global prescription drug revenue by 2030) (<sup>[6]</sup> [www.dcatvci.org](http://www.dcatvci.org)) (<sup>[7]</sup> [www.dcatvci.org](http://www.dcatvci.org)). Innovations such as gene therapy, enzyme replacement, and targeted small-molecule drugs have led to breakthrough treatments for a subset of rare disorders, transforming previously lethal diseases (e.g. spinal muscular atrophy, cystic fibrosis) into manageable conditions. However, developing treatments for ultra-rare diseases remains challenging due to scientific, economic, and [regulatory hurdles](#).
- **Case Studies:** Several real-world examples illustrate both the successes and challenges in rare diseases:

- **Spinal Muscular Atrophy (SMA):** Once the leading genetic cause of infant death, SMA now has multiple effective therapies (an antisense oligonucleotide, a gene therapy, and a small-molecule splicing modifier). Treated infants who 5–10 years ago would have died by age 2 are now surviving and achieving developmental milestones [<https://investors.biogen.com/news-releases/news-release-details/new-results-landmark-nurture-study-show-pre-symptomatic-sma>].
- **Cystic Fibrosis (CF):** A rare genetic disease that historically led to early mortality (median survival ~30 years). New CFTR modulator drugs (e.g. Trikafta/Kaftrio) have dramatically improved lung function and could extend median lifespans toward normal (70–80+ years) for many patients starting therapy early (<sup>[8]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)) (<sup>[9]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)).
- **Progeria:** An ultra-rare premature-aging disease with median life expectancy of 14 years. In 2020, the first treatment (lonafarnib) was approved, shown to extend lifespan by ~2.5 years on average [<https://www.biospace.com/article/giving-the-gift-of-time-fda-approves-first-treatment-for-rapidly-aging-children/>].
- **Personalized Medicine (N-of-1):** In 2018, researchers custom-designed an antisense oligonucleotide for a single patient with Batten's disease, halting the neurodegeneration in that child – a pioneering example of individually tailored therapy [<https://www.nejm.org/doi/full/10.1056/NEJMoa1813279>]. While not yet scalable, this case opened doors for compassionate "N-of-1" [drug development](#) for ultra-rare conditions.
- **Economic and Social Impact:** Rare diseases carry enormous economic burdens. A 2022 study estimated the total economic cost of rare diseases in the U.S. alone at nearly \$1 trillion per year (for just 379 analyzed diseases) when including direct medical costs (~\$449B) and indirect costs such as lost productivity (~\$548B) (<sup>[10]</sup> [ojrd.biomedcentral.com](https://www.ojrd.biomedcentral.com)) (<sup>[11]</sup> [ojrd.biomedcentral.com](https://www.ojrd.biomedcentral.com)). Patients and families often incur high out-of-pocket expenses for specialized care, and caregivers may forgo employment to provide care, leading to financial hardship. Quality of life is severely affected; chronic pain, disability, and psychological stress are common. Despite these burdens, historically rare diseases have struggled to attract proportional research funding and healthcare resources, though this is beginning to change.
- **Global Policy and Future Directions:** The recognition of rare diseases as a public health priority is at an all-time high. By 2025, over 30 countries have national rare disease plans or strategies [<https://www.ojrd.biomedcentral.com/articles/10.1186/s13023-018-0935-9>], aiming to improve coordination of care and research. The World Health Assembly's 2025 resolution calls on the World Health Organization to create a global action plan for rare diseases (<sup>[4]</sup> [www.rarediseasesinternational.org](https://www.rarediseasesinternational.org)), fostering international collaboration. Future efforts will likely focus on: **(a)** expanding genetic newborn screening and diagnostic programs to end the diagnostic odyssey; **(b)** incentivizing development of therapies for the ~95% of diseases still lacking treatment (e.g. through public-private partnerships, novel clinical trial designs, and platforms for drug repurposing); **(c)** leveraging technologies like gene editing (CRISPR), mRNA therapies, and AI-driven drug discovery to target rare diseases more efficiently; and **(d)** enhancing healthcare system readiness to ensure equity of access to costly orphan therapies across all regions. The goal is that in the coming decade, no person living with a rare disease is left without a diagnosis or treatment option solely due to the rarity of their condition.

In summary, the landscape of rare diseases in 2025 is characterized by both hopeful progress and persistent challenges. Major strides in science, medicine, and policy have saved lives and brought new treatments to patients who previously had none. At the same time, the vast majority of rare disease patients are still awaiting breakthroughs. The community of stakeholders – patients, families, clinicians, scientists, industry, and policymakers – is more mobilized than ever to address these gaps. Continued multi-sector collaboration and innovation will be essential to translating the advances of today into a future where rare diseases are diagnosed promptly, treated effectively, and ultimately, where "rare" no longer means ignored.

## Introduction and Background

**Defining Rare Diseases:** A rare disease (also called an "orphan" disease) is generally defined as a condition that affects a small fraction of the population. Different jurisdictions specify different prevalence thresholds for "rare." In the United States, a disease affecting fewer than 200,000 Americans (about 1 in 1,600 people) qualifies as rare under the Orphan Drug Act of 1983 [<https://www.fda.gov/media/119283/download>]. The European Union defines rare diseases as those affecting no more than 5 in 10,000 people (0.05% of the EU

population) [[https://ec.europa.eu/health/sites/default/files/files/orphanmp/doc/orphan\\_regulation\\_en.pdf](https://ec.europa.eu/health/sites/default/files/files/orphanmp/doc/orphan_regulation_en.pdf)]. Japan's definition is a condition affecting <50,000 patients in Japan (~1 in 2,500) [<https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0935-9>]. Despite differences in definition, all share the concept of rareness and the consequent need for special efforts to promote drug development – hence the term “orphan” diseases, as pharmaceutical companies historically neglected them due to limited market potential.

**Scope and Scale:** While each rare disease affects relatively few people, there are thousands of distinct rare diseases. As medical science has advanced, the number of recognized rare disorders has grown to over 6,000 (some sources say up to ~7,000) (<sup>[12]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)) ([projects.research-and-innovation.ec.europa.eu](https://projects.research-and-innovation.ec.europa.eu)). Collectively, rare diseases are estimated to affect between 3.5% and 8% of the global population. A rigorous analysis by Orphanet and colleagues in 2019 estimated point prevalence at 3.5–5.9% worldwide – roughly **300 million people** based on a world population of 7.5 billion (<sup>[1]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)). Other analyses, including CDC and patient advocacy groups, cite figures up to 400 million or more globally when including currently undiagnosed cases (<sup>[13]</sup> [www.weforum.org](http://www.weforum.org)) (<sup>[14]</sup> [blogs.cdc.gov](https://blogs.cdc.gov)). For context, if all rare disease patients constituted a single country, it would be the third largest country in the world in population. In the United States, rare diseases affect an estimated 25–30 million Americans (approximately 1 in 10) (<sup>[14]</sup> [blogs.cdc.gov](https://blogs.cdc.gov)), and in Europe around 30 million people (about 1 in 17 Europeans) ([projects.research-and-innovation.ec.europa.eu](https://projects.research-and-innovation.ec.europa.eu)). These numbers underscore the paradox that rare diseases, taken together, are not rare at all – they are a significant public health concern globally.

**Characteristics of Rare Diseases:** About 72–80% of rare diseases are believed to have a genetic basis (<sup>[12]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)). Most are inherited in a Mendelian (single-gene) fashion, while some result from new mutations or chromosomal abnormalities. The remaining rare diseases include rare cancers, rare infectious diseases, and idiopathic conditions. Many rare diseases are severe, chronic, and multisystem disorders. Approximately 70% of rare diseases manifest in **childhood** (<sup>[12]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)), often from birth or early infancy. These pediatric-onset rare diseases contribute heavily to infant and child mortality and long-term disability. It is estimated that rare genetic disorders account for 10–15% of infant deaths in developed countries [<https://pubmed.ncbi.nlm.nih.gov/33200345/>], and sadly around 30% of children with a rare disease will die by age 5 (<sup>[13]</sup> [www.weforum.org](http://www.weforum.org)). The clinical course varies widely: some conditions are degenerative and life-limiting (for example, Tay-Sachs disease leads to death in early childhood), whereas others are compatible with a normal lifespan but with significant morbidity (such as many rare autoimmune disorders).

Rare diseases also tend to be complex, multi-organ conditions that require specialized care. Patients often suffer not only from the primary effects of the disease but also secondary complications (e.g. orthopedic issues in skeletal dysplasias, organ damage in metabolic diseases) and psychosocial burdens. The rarity of each disease means that clinical expertise and research knowledge are limited and geographically dispersed. This often leaves patients and families feeling isolated and struggling to find information and effective care.

**Historical Neglect:** The term “orphan disease” arose to describe these conditions that were “orphans” of the healthcare system – largely overlooked in medical research and drug development due to their low prevalence. For much of the 20th century, progress on rare diseases was sporadic and driven mainly by academic curiosity or individual clinician-scientists. Patients with rare conditions frequently had no established diagnosis (their disorders might not even have had a name) and certainly few prospects for treatment. For the pharmaceutical industry, investing in therapies for small patient populations was seen as financially unviable, since the cost of developing and marketing a new drug could not be recovered from sales in a tiny market. Consequently, very few drugs for rare diseases were developed prior to the 1980s, and those that did exist were often discovered serendipitously or repurposed from other uses (for example, corticosteroids to alleviate symptoms in Duchenne muscular dystrophy, or dietary modifications like low-protein diets for phenylketonuria).

**Growing Recognition:** By the late 20th century, a confluence of factors began to change the landscape. Advances in medical genetics were identifying the molecular causes of many previously mysterious disorders, galvanizing hope that targeted treatments could be developed. At the same time, patient advocacy groups started to organize and demand action. A pivotal movement occurred in the U.S. in the late 1970s and early 1980s, led by patient activists and organizations like the National Organization for Rare Disorders (NORD, founded 1983). These advocates highlighted real-life stories of patients unable to get life-saving drugs because there was no financial incentive for companies to produce them (for instance, drugs for rare metabolic disorders that were shelved despite promising results). Public awareness campaigns and testimony before Congress painted the neglect of rare disease patients as a moral issue. This advocacy culminated in the landmark **Orphan Drug Act of 1983** in the United States.

**Orphan Drug Act and Its Impact:** The U.S. Orphan Drug Act (ODA) established financial and regulatory incentives to encourage companies to develop therapies for rare diseases. Key provisions included: 7-year market exclusivity for approved orphan indications (meaning no direct competitor can market the same drug for that indication during that period), tax credits covering 50% (later 25%) of clinical trial costs, fee waivers for FDA applications, and research grants for orphan drug development [<https://www.fda.gov/media/119283/download>]. The ODA was a turning point – in the decade before 1983, only about 10 treatments for rare diseases reached the market ([projects.research-and-innovation.ec.europa.eu](https://projects.research-and-innovation.ec.europa.eu)). In the decade after, dozens of orphan drugs were developed, and the trajectory has continued upward. As of 2024, the FDA has granted over **6,000** orphan designations (drugs in development for rare diseases) and more than **1,000** orphan drug products have been approved for marketing in the U.S. ([www.ome.bio](http://www.ome.bio)). This reflects an enormous increase in innovation spurred by the ODA. Importantly, each approved orphan drug can dramatically change outcomes for the affected patients – turning formerly untreatable diseases into manageable ones.

Other countries followed suit. **Japan** instituted orphan drug policies by the early 1990s (with incentives like 10-year market exclusivity and subsidies for R&D) [<https://ojrd.biomedcentral.com/articles/10.1186/s13023-018-0935-9>]. **Australia, Canada,** and other nations adopted definitions and policies to facilitate orphan drug development, often aligning with either U.S. or EU criteria. By 2000, the **European Union** implemented its Orphan Medicinal Products Regulation (EC No. 141/2000) which provided incentives akin to the U.S. – including **10-year market exclusivity** for orphan drugs in the EU, fee reductions from the European Medicines Agency (EMA), and research support [[https://ec.europa.eu/health/sites/default/files/files/orphanmp/doc/orphan\\_regulation\\_en.pdf](https://ec.europa.eu/health/sites/default/files/files/orphanmp/doc/orphan_regulation_en.pdf)]. The EU also created the **Committee on Orphan Medicinal Products (COMP)** to oversee orphan designations. The impact in Europe has also been significant, though somewhat lagging the U.S. in sheer numbers. Between 2000 and early 2024, the EMA received ~2,900 orphan designation applications and approved around **150 orphan medicines** for marketing in Europe (<sup>[15]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)) (<sup>[16]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)). These include therapies for rare cancers, metabolic disorders, immunological diseases, and more.

**Global Advocacy and Collaboration:** Alongside legislation, rare diseases benefitted from growing global collaboration. In 2008, patient groups established **Rare Disease Day** – observed on February 29 (a “rare” date) or Feb 28 – to raise awareness worldwide. Advocacy networks blossomed, such as **EURORDIS** (Rare Diseases Europe) representing patient organizations across Europe, and **Rare Diseases International (RDI)** as a global alliance. In 2011, major research funders launched the **International Rare Diseases Research Consortium (IRDiRC)**, uniting public and private stakeholders across Asia, Europe, and the Americas to share data and strategies. IRDiRC set ambitious goals: for example, its initial goal (2011–2020) aimed for **200 new rare disease therapies** and diagnostic tools for most rare diseases by 2020. This goal was dramatically exceeded – over 770 orphan drugs were approved globally during that period [<https://www.nature.com/articles/d41573-021-00185-7>] – leading IRDiRC to set new goals for 2017–2027: **1000 new therapies** for rare diseases, diagnosis within one year for all patients with a known rare disease, and new methods to measure patient outcomes (<sup>[17]</sup> [irdirc.org](https://irdirc.org)).

This introduction provides the foundation for understanding why rare diseases have become a significant medical and societal issue. The following sections will delve deeper into the current 2025 landscape: from the

epidemiology and burden of rare diseases, to the challenges in diagnosis and treatment development, to case studies illustrating recent progress, and a look ahead at emerging solutions and policies.

Before exploring these topics in detail, **Table 1** summarizes some key facts about rare diseases globally, as established by recent research and reports:

**Table 1: Global Overview of Rare Disease Key Facts (2025)**

Metric	Statistic (2025)	Source
Number of identified rare diseases	>6,000 distinct conditions (up to ~7,000)	Orphanet/EURORDIS <sup>[12]</sup> <a href="http://www.rarediseasesinternational.org">www.rarediseasesinternational.org</a> ( <a href="http://projects.research-and-innovation.ec.europa.eu">projects.research-and-innovation.ec.europa.eu</a> )
Global population affected	~300 million (3.5–5.9% of world population)	RDI / Eur. Journal of Human Genetics <sup>[1]</sup> <a href="http://www.rarediseasesinternational.org">www.rarediseasesinternational.org</a>
U.S. population affected	~25–30 million (≈1 in 10 Americans)	CDC / NIH Genetics [ <a href="https://blogs.cdc.gov/genomics/2019/04/04/introducing-the-rare-diseases/">https://blogs.cdc.gov/genomics/2019/04/04/introducing-the-rare-diseases/</a> ]
European population affected	~30 million (≈1 in 17 Europeans)	EURORDIS / EC data ( <a href="http://projects.research-and-innovation.ec.europa.eu">projects.research-and-innovation.ec.europa.eu</a> )
Proportion genetic in origin	~72% (over 70% have genetic cause)	Orphanet analysis <sup>[12]</sup> <a href="http://www.rarediseasesinternational.org">www.rarediseasesinternational.org</a>
Onset in childhood	~70% begin in childhood (pediatric onset)	Orphanet analysis <sup>[12]</sup> <a href="http://www.rarediseasesinternational.org">www.rarediseasesinternational.org</a>
Average diagnostic delay	~4.5 years (from first symptoms to diagnosis on average)	EURORDIS survey 2022 [ <a href="https://www.nature.com/articles/s41431-024-01604-z">https://www.nature.com/articles/s41431-024-01604-z</a> ]
% of rare diseases with <b>no</b> approved treatment	~95% lack an FDA-approved or EMA-approved treatment	IRDiRC/Horizon Report ( <a href="http://projects.research-and-innovation.ec.europa.eu">projects.research-and-innovation.ec.europa.eu</a> )
Number of FDA-approved orphan drugs	~1,000 (since 1983 to 2024)	U.S. FDA OOPD data ( <a href="http://www.ome.bio">www.ome.bio</a> )
Number of EMA-approved orphan drugs	~150 (since 2000 to early 2024)	EMA COMP report <sup>[16]</sup> <a href="http://pmc.ncbi.nlm.nih.gov">pmc.ncbi.nlm.nih.gov</a>
Pediatric mortality impact	~30% of rare disease children die by age 5	World Economic Forum <sup>[3]</sup> <a href="http://www.weforum.org">www.weforum.org</a>
Economic burden (U.S.)	~\$997 billion/year (direct + indirect costs, for 379 diseases)	OJRD 2022 study <sup>[11]</sup> <a href="http://ojrd.biomedcentral.com">ojrd.biomedcentral.com</a> <sup>[18]</sup> <a href="http://ojrd.biomedcentral.com">ojrd.biomedcentral.com</a>

*Table Note:* Prevalence and population figures can vary by source. The ~300 million global figure is a conservative estimate for identified cases <sup>[1]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)); some sources estimate up to 400 million when including undiagnosed patients <sup>[13]</sup> [www.weforum.org](http://www.weforum.org)). Diagnostic delay is an average; many patients experience much longer odysseys <sup>[19]</sup> [www.eurordis.org](http://www.eurordis.org)). The economic burden cited for the U.S. (2019 data) highlights that rare diseases collectively have a cost impact comparable to common chronic diseases <sup>[20]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)).

These statistics frame the considerable challenge and urgency in addressing rare diseases. In the next sections, we explore the landscape in detail: starting with epidemiology and the everyday challenges patients face in obtaining a diagnosis and care.

# Epidemiology and Burden of Rare Diseases

Understanding the epidemiology of rare diseases is inherently challenging due to their low prevalence and often limited data. However, research efforts like the Orphanet database and national rare disease registries have shed light on how these diseases affect populations.

**Global Prevalence:** As noted, rare diseases in aggregate affect roughly 4% (ranging 3.5–5.9%) of the world's population at any time (<sup>[1]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)). This equates to approximately 300 million people worldwide, a number comparable to the population of the United States. It is striking that although each rare disease might affect only one in thousands or millions of people, when added together rare diseases are as prevalent as more familiar public health issues. For instance, the global rare disease population is several times larger than the worldwide HIV/AIDS population and on par with the number of people living with diabetes. This comparison has led public health experts to argue that rare diseases must be seen as a **collective public health priority** rather than isolated medical curiosities (<sup>[21]</sup> [www.weforum.org](http://www.weforum.org)).

**Distribution and Examples:** Rare diseases do not affect all populations equally. Some rare diseases are truly pan-ethnic (appearing worldwide), while others show higher prevalence in certain ethnic groups or regions due to genetic founder effects or environmental factors. For example:

- **Sickle Cell Disease** is a rare disease in much of the world but more common among individuals of African or Mediterranean descent due to historical malaria-related gene selection; in parts of sub-Saharan Africa, sickle cell is not rare at all, whereas in North America it qualifies as an orphan disease (affecting ~100,000 people in the U.S.) [<https://www.cdc.gov/ncbddd/sicklecell/data.html>].
- **Tay-Sachs disease** (a rare neurodegenerative disease) is more frequent in Ashkenazi Jewish populations (carrier rate ~1 in 30), though still rare in absolute terms.
- **Thalassemias** are rare in northern Europe but relatively common genetic disorders in South Asia and the Middle East.
- **The "Finnish disease heritage"** is a term describing about 35 rare genetic diseases that have higher incidence in Finland due to founder mutations (e.g., congenital nephrosis).
- **Rare infectious diseases** can cluster regionally; for instance, **Bolivian hemorrhagic fever** is exceedingly rare globally but found in a specific area of Bolivia.

These examples illustrate that "rare" can be context-dependent. However, the vast majority of rare diseases are uniformly sparse in the population and do not have such geographic clustering – they occur randomly and infrequently worldwide.

**Ultra-Rare Diseases:** Within the rare disease universe, there is a subset often termed "ultra-rare" diseases – conditions with only a few hundred known cases or even fewer. Many metabolic disorders, neuromuscular disorders, and developmental syndromes fall in this category. For example, **Hutchinson-Gilford Progeria Syndrome (progeria)** has a prevalence of roughly 1 in 20 million (only ~400 known cases worldwide) (<sup>[22]</sup> [www.biospace.com](http://www.biospace.com)). Another example, **fibrodysplasia ossificans progressiva** ("stone man syndrome"), has about 800 confirmed cases globally. These ultra-rare conditions pose particular challenges for research and drug development, as even finding enough patients for a clinical trial can be difficult. From an epidemiological standpoint, ultra-rare diseases contribute only a tiny fraction to the total rare disease population; the bulk of the 300 million patients are accounted for by the "less rare" rare diseases (those affecting, say, tens of thousands worldwide, like cystic fibrosis or Duchenne muscular dystrophy). Yet, each ultra-rare disease is a complete world for the patients and families affected, underscoring the ethical imperative to not ignore anyone due to rarity.

**Lack of Epidemiological Data:** A major challenge in rare disease epidemiology is under-diagnosis and under-reporting. Many patients suffer for years without a diagnosis or are misdiagnosed with more common conditions. Especially in low- and middle-income countries, diagnostic capabilities for rare diseases (such as genetic testing) may be limited, meaning many cases are never identified as rare diseases in the first place. Consequently, the true prevalence of various rare diseases is often unknown or underestimated. For example, rare disorders like **Ehlers-Danlos syndrome (EDS)** or **mast cell activation syndrome** are thought to be underdiagnosed due to variable presentation and limited awareness. To address this gap, initiatives like national rare disease registries and the Orphanet database collect epidemiological information. The Orphanet database compiles prevalence and incidence figures from literature for thousands of rare diseases, providing a valuable (if imperfect) resource for understanding how many people are affected by each condition [[https://www.orpha.net/orphacom/cahiers/docs/GB/Epidemiology\\_of\\_rare\\_diseases\\_in\\_member\\_states.pdf](https://www.orpha.net/orphacom/cahiers/docs/GB/Epidemiology_of_rare_diseases_in_member_states.pdf)].

From the Orphanet analysis published in 2019, of the 6,000+ rare diseases, about 149 diseases each have a prevalence over 1 per 100,000 (these tend to be the more “common” rare diseases such as congenital deafness, some rare cancers, etc.), while the vast majority have much lower prevalence (<sup>[23]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)). Interestingly, about 20% of rare diseases are responsible for 80% of the rare disease patient population – meaning a small subset of the better-known rare diseases accounts for a large share of patients. These include conditions like:

- **Cystic Fibrosis (CF):** ~70,000 cases worldwide (about 30,000 in the U.S. and 40,000 in Europe) [<https://www.cff.org/what-is-cystic-fibrosis/>].
- **Hemophilia:** Over 400,000 globally (hemophilia A & B combined), though still meeting rare criteria in individual countries [<https://www.wfh.org/en/resources/global-survey/>].
- **Thalassemia major:** Tens of thousands of patients worldwide (especially in Asia/Mediterranean).
- **Duchenne Muscular Dystrophy (DMD):** ~1 in 3,500 male births; global prevalence around 30,000–50,000.
- **Scleroderma:** ~150,000 worldwide (considered rare).
- **Certain rare cancers** like *pediatric leukemias* or *thyroid cancer* – while “rare” by incidence, they accumulate significant prevalence.

On the other hand, the majority of rare diseases may have only dozens to a few hundred known patients each (e.g., the ultra-rare metabolic and genetic syndromes). These ultra-rare conditions cumulatively have fewer patients, but their diversity means each demands specific attention.

**Natural History and Severity:** Epidemiology goes beyond prevalence to consider the natural history (disease course) and outcomes of rare diseases. Many rare diseases are progressive and serious. For example:

- *Spinal muscular atrophy type 1* leads to inability to sit and death by age 2 in >90% of cases without treatment (<sup>[24]</sup> [smanewstoday.com](https://www.smanewstoday.com/)).
- *Untreated phenylketonuria (PKU)* results in severe intellectual disability, but with early dietary treatment patients can live relatively normal lives – highlighting how intervention changes epidemiologic outcomes.
- *Fabry disease* (a rare lysosomal storage disorder) historically caused kidney failure and strokes in mid-adulthood; enzyme replacement therapy introduced in 2001 improved life expectancy, though patients still have a shortened lifespan and burden of illness.
- *Rare cancers:* The epidemiology of rare cancers (like sarcomas, certain leukemias) is often tracked separately by oncology groups. Rare cancers collectively account for about 22% of all cancer cases, indicating that “rare” cancers are a significant fraction of the cancer burden [[https://ec.europa.eu/health/sites/health/files/state/docs/health\\_glance\\_2016\\_refocus\\_rarediseases\\_en.pdf](https://ec.europa.eu/health/sites/health/files/state/docs/health_glance_2016_refocus_rarediseases_en.pdf)].

Crucially, rare diseases often impose a high burden of illness on patients and families. For instance, a child with a rare neurodegenerative disease might require 24/7 care, frequent hospitalizations, and expensive supportive

treatments (ventilators, feeding tubes, physical therapy). The quality of life for both patient and caregivers is typically very low without appropriate support. Epidemiological studies of quality of life consistently show that rare disease patients have worse health-related quality of life scores than the general population and often worse than patients with more common chronic diseases

[<https://ojrd.biomedcentral.com/articles/10.1186/s13023-022-02256-2>]. This is due to the combination of severe physical symptoms, lack of effective treatments, and psychosocial stressors (isolation, uncertainty, financial strain).

**Geographical Disparities:** There is also a disparity in the rare disease burden by geography in terms of outcomes. Patients in high-income countries generally have better access to diagnostic tools and any available treatments, whereas patients in low-income regions may never receive a proper diagnosis or therapy. A rare genetic disease that is treatable (e.g., with specific drugs or transplant) in wealthy countries might be a death sentence in a resource-limited setting purely due to lack of access. One stark example is **lysosomal storage diseases** (like Gaucher, Fabry, Pompe disease): enzyme replacement therapies exist and are standard of care in Europe/US (albeit extremely expensive), yet in many developing countries these drugs are not available or affordable, so patients go untreated. This creates an epidemiologic divergence – the life expectancy for these diseases has improved where treatment is available, but remains poor elsewhere. The recent WHO resolution in 2025 explicitly mentions equity and inclusion, aiming to reduce such global disparities in rare disease care (<sup>[25]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)) (<sup>[4]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)).

In summary, the epidemiological landscape of rare diseases in 2025 is one where:

- Rare diseases collectively are common enough to demand significant healthcare attention (~300 million affected globally).
- Data collection is improving but many cases still go unrecognized.
- A minority of rare diseases account for a majority of patients, yet every rare disease has unique importance.
- The burden of rare diseases is heavy in terms of mortality, morbidity, and quality of life.
- There are pronounced gaps between what is possible in best-case scenarios (early diagnosis, advanced treatments in top centers) and what many patients actually experience, especially across different regions.

The next section will delve into one of the most defining challenges for rare diseases: the **diagnostic journey** – why it takes so long for many patients to get diagnosed and what is being done to improve this situation.

## Challenges in Rare Disease Diagnosis

Obtaining an accurate diagnosis is often the first and most formidable challenge faced by individuals with rare diseases. This section explores why diagnostic delays are so common and the efforts underway to address them.

**The Diagnostic Odyssey:** Rare disease patients frequently endure a long and arduous journey before receiving a correct diagnosis. This journey is so characteristic that it's termed the "diagnostic odyssey" in medical literature. On average, it takes several **years** from the onset of symptoms to the final diagnosis for rare diseases. A large international survey published in 2024 (the EURORDIS Rare Barometer survey) found an average delay of **4.7 years** in Europe (<sup>[19]</sup> [www.eurordis.org](http://www.eurordis.org)). Other studies have reported similar or even longer timeframes in different regions (commonly 5-8 years in the United States and Europe) [<https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01303-7>]. It's not uncommon for patients to receive multiple misdiagnoses along the way. For example, a person with a rare autoimmune syndrome might be misdiagnosed as having a psychosomatic illness, or a child with an inherited metabolic disorder might be mistaken for having cerebral palsy.

Several factors contribute to these protracted diagnostic timelines:

- **Limited Physician Awareness:** Most doctors have never encountered the specific rare disease a patient has, simply because each condition is so uncommon. A survey in China found that only ~5% of physicians felt moderately or well informed about rare diseases, and 93% of physicians acknowledged that rare disease patients are difficult to manage due to their lack of familiarity ([<sup>26</sup> pmc.ncbi.nlm.nih.gov]) ([<sup>27</sup> pmc.ncbi.nlm.nih.gov]). Similarly, surveys in other countries reveal that front-line healthcare providers often are not trained to recognize rare conditions. When a condition is outside a doctor's experience, symptoms may be attributed to more common ailments. For instance, periodic paralysis in a rare genetic disorder might be misdiagnosed as epilepsy or conversion disorder by an unaware physician.
- **Nonspecific or Variable Symptoms:** Many rare diseases present with symptoms that overlap with common conditions, or they manifest in a highly variable way. Take **Ehlers-Danlos syndrome (EDS)**, a rare connective tissue disorder: its symptoms of joint pain, hyperflexibility, and fatigue can be dismissed as benign or misattributed to fibromyalgia for years before the connective tissue disorder is recognized. In the Rare Barometer survey, about 30% of patients felt that their diagnosis was delayed due to doctors initially attributing symptoms to more common conditions or not realizing the constellation indicated a rare disease ([<sup>28</sup> pmc.ncbi.nlm.nih.gov]).
- **Fragmented Consultations:** Patients often see numerous specialists in different fields as they chase answers. One analysis showed rare disease patients in Europe consulted an average of 7.3 physicians and received 2-3 misdiagnoses before the correct one ([<sup>5</sup> www.eurordis.org]). Each specialist may focus on their organ system, potentially missing the broader syndrome. For example, a patient with an inborn error of metabolism might see a neurologist for seizures, a gastroenterologist for feeding problems, and a pulmonologist for breathing issues – and unless someone pieces these together holistically (often a geneticist or a rare disease specialist), the root cause might be missed.
- **Access to Genetic Testing:** Many rare diseases require specialized tests (genetic testing, biomarker assays, etc.) for confirmation. Until recently, such tests were not widely available or were very expensive. Even now, access can be limited by healthcare coverage. In some cases, patients are not offered genetic testing due to physician unfamiliarity or assumptions about cost. In middle- and low-income countries, advanced diagnostics like whole exome sequencing might be scarce. The availability of next-generation sequencing in the 2010s has begun to revolutionize diagnosis, enabling “diagnostic odyssey ending” for some who get their genome sequenced after years of mystery. For instance, the 100,000 Genomes Project in the UK demonstrated that broad genomic testing can diagnose a significant fraction of previously unsolved rare disease cases [<https://www.genomicsengland.co.uk/understanding-genomic-medicine/rare-disease>].
- **Disease Rarity Itself:** By definition, a rare disease might not even be described in medical literature when a patient first presents. New rare diseases are still being discovered – especially as genetic research identifies previously unknown disorders. A patient could essentially be the first known case of an ultrarare condition, meaning even the best doctor would struggle to diagnose it without research context. In the past decade, thousands of new rare genetic syndromes have been delineated via exome sequencing efforts. While this is a scientific triumph, it implies that patients with those conditions born before these discoveries often spent years undiagnosed.

**Consequences of Diagnostic Delay:** The impact of delayed diagnosis is severe. Without a name for their condition, patients often do not receive appropriate management (even symptomatic treatments or supportive care) and may undergo unnecessary or harmful interventions. Families describe enormous psychological distress during the years of uncertainty – not knowing if a child's condition has a name or what to expect. In some cases, a correct diagnosis opens the door to a treatment that was missed for years. For example, children with *spinal muscular atrophy* prior to 2016 had no treatment, but since therapies became available, getting diagnosed early is critical to receive life-saving interventions. A delay of even a few months in such cases can mean the difference between reversible symptoms and permanent disability. Another example: *Pompe disease*

(a rare muscle disorder) can be treated by enzyme replacement, but delays in diagnosis lead to irreversible muscle damage that therapy cannot fully undo. Therefore, diagnosing early can literally save or extend lives and improve outcomes. Conversely, a missed or wrong diagnosis can result in interventions that are not only futile but potentially harmful – e.g., a child misdiagnosed with a seizure disorder might be on strong anti-seizure medications needlessly, while the underlying metabolic stroke continues unchecked.

Diagnostic delay also has economic consequences: families often incur huge costs going from doctor to doctor, traveling to specialty centers, and paying for tests. One U.S. study found that rare disease patients had significantly higher medical costs in the years leading up to diagnosis, essentially “search costs” of the odyssey [<https://ojrd.biomedcentral.com/articles/10.1186/s13023-022-02256-2>]. Additionally, parents might stop working to manage their undiagnosed child’s needs, and the stress can fracture family dynamics. Simply obtaining a diagnosis – even if no cure exists – is frequently described by patients as a relief, because it validates their experience and allows connection with disease-specific support groups.

**Improvements and New Tools:** Recognizing the diagnostic challenge, various initiatives and tools have been developed:

- **Newborn Screening (NBS):** Newborn screening programs test infants shortly after birth for certain treatable rare diseases (using a blood spot test). Historically focused on metabolic disorders like PKU, many countries have expanded their NBS panels to include dozens of rare conditions that have interventions (e.g., congenital hypothyroidism, sickle cell disease, cystic fibrosis, medium-chain acyl-CoA dehydrogenase deficiency). In the US, for instance, the Recommended Uniform Screening Panel (RUSP) now includes spinal muscular atrophy (SMA) and severe combined immunodeficiency (SCID), among others, because early detection can enable life-saving treatment (SMA gene therapy or SCID bone marrow transplant) before symptoms manifest. Newborn screening has been one of the public health success stories for rare diseases – conditions like PKU which once caused rampant disability are now caught at birth and managed with diet, allowing normal development. However, NBS covers only a fraction of rare diseases (generally those with a known, effective early treatment and a relatively high frequency). As treatments expand, there are proposals to add more rare diseases to newborn screening. Some experts even envision genomic sequencing of newborns in the future to screen for a wider array of genetic disorders – pilot programs in the UK and US are currently studying the feasibility of newborn genome sequencing [<https://www.genomicsengland.co.uk/news/uk-newborn-genomes-programme-announcement>].
- **Genomic Sequencing Programs:** Beyond newborns, many countries have initiatives for undiagnosed patients of any age. Examples include the NIH Undiagnosed Diseases Program (UDP) in the U.S., which brings together experts to solve cases that have eluded diagnosis, often using whole genome sequencing and deep phenotyping. The UDP boasts a diagnostic rate of ~35% for previously unsolved cases, uncovering new rare diseases in the process [<https://undiagnosed.hms.harvard.edu/>]. Similar undiagnosed disease networks exist internationally and share data via platforms like the Matchmaker Exchange, which connects clinicians/scientists worldwide who have patients with similar mysterious conditions to identify new syndromes. Such global data-sharing has led to the discovery of many novel rare disease genes in the last few years.
- **Artificial Intelligence (AI) and Decision Support:** AI tools are emerging to assist in diagnosing rare diseases. For example, deep learning algorithms can analyze photographs of a patient’s face to detect dysmorphic features characteristic of certain genetic syndromes (one such tool is Face2Gene). AI-driven symptom checkers and diagnostic decision support systems can also flag rare disease possibilities that a physician might not think of. There are cases where an AI system suggested a correct rare diagnosis (like **Menkes disease**) based on pattern recognition, aiding doctors in confirming it [<https://www.bbc.com/news/technology-50228201>]. While still in early stages, these technologies hold promise in speeding up recognition.
- **Education and Guidelines:** Medical curricula and continuing education are increasingly including rare disease awareness. For instance, some countries have instituted rare disease centers of excellence that not

only treat patients but also disseminate guidelines to general practitioners. European Reference Networks (ERNs) in the EU connect specialists across countries for groups of rare diseases (such as metabolic disorders, bone disorders, etc.) to improve diagnostic pathways and care. The idea is that a local doctor can consult an ERN center remotely for advice on a challenging case. Additionally, clinical practice guidelines are being developed for certain rare diseases to guide physicians on when to suspect them and how to confirm the diagnosis. An example is a guideline on recognizing **fabry disease** in patients with unexplained kidney & heart issues.

- **Patient Advocacy Role:** Interestingly, patient advocacy groups often play a direct role in diagnosis. Many families, after struggling through normal medical channels, turn to online communities or rare disease organizations. Through networking, they might find a description of a similar case or be pointed to a specialist. In an era of internet connectivity, some patients have essentially self-diagnosed by comparing their symptoms with online rare disease databases or by pushing for specific genetic tests after doing personal research. While this can sometimes lead down wrong paths, it also has empowered patients to be active in the diagnostic process.

**Persistent Gaps:** Despite progress, challenges remain. Some rare diseases still require invasive tests (like muscle or liver biopsies) which may not be done until late in the disease course. Others might be diagnostically obvious only in advanced stages – early on they mimic common issues. Overcoming cognitive bias in medicine (the tendency to diagnose common conditions and overlook rare ones) is tough; there's a saying, "When you hear hoofbeats, think horses not zebras," which is taught to medical trainees to avoid overzealous rare diagnoses. Rare disease advocates have embraced the zebra as a symbol, precisely to counter that adage, reminding clinicians that "sometimes it really is a zebra." Efforts like the **Global Commission to End the Diagnostic Odyssey** (launched by Shire, Microsoft, EURORDIS) have called for systematic changes, including better use of technology and cross-border collaboration, to cut the time to diagnosis in half [<https://www.end-rare-disease-diagnosis.com/>].

In conclusion, while the diagnostic outlook for rare diseases in 2025 is better than it was a decade ago – thanks to genomics, new screening, and awareness – it is still unacceptably slow in many cases. The average multi-year wait and multiple misdiagnoses constitute not just a medical issue but a profound human and social problem. Reducing the diagnostic delay is a top priority because it is the gateway to any other form of care or treatment. As one advocate aptly put it: "You can't treat a disease you haven't diagnosed."

With diagnosis in hand, the next challenge is equally daunting: the quest for treatments. In the following section, we will examine the landscape of rare disease treatment development, including why 95% of rare diseases still lack an approved therapy and what strategies are being employed to change that.

## Therapeutic Landscape: Drug Development and Treatment of Rare Diseases

Development of effective treatments for rare diseases (often called **orphan drugs**) is a central challenge in the field. Despite significant progress since the 1980s, the vast majority of rare diseases have no cure or specific therapy. Here we explore the current state of rare disease therapeutics, including success stories, development hurdles, and trends in innovation.

**The 5% Reality:** It has been consistently estimated that only around **5% of rare diseases have an FDA-approved treatment** ([projects.research-and-innovation.ec.europa.eu](https://projects.research-and-innovation.ec.europa.eu)). Put differently, for approximately 19 out of 20 rare diseases, there is no approved medication specifically targeting the disease. This statistic illustrates a "treatment gap" affecting thousands of conditions. Even among the roughly 5% of rare diseases that do have a therapy, many are *not* curative but only partially effective or symptom-relieving. For example, corticosteroids are

used in Duchenne muscular dystrophy to slow muscle degeneration, but they are not a cure. True disease-modifying or curative treatments exist for only a handful of rare diseases. As of 2025, areas where notable therapeutic successes have been achieved include certain enzyme deficiencies, some immune disorders, and a few neurological and metabolic diseases (often through innovative modalities like gene therapy, as discussed below). However, entire categories like most rare neurodegenerative diseases, congenital anomalies, or ultra-rare metabolic conditions remain without any approved drugs.

**Regulatory Incentives and Orphan Drug Approvals:** As described earlier, orphan drug legislation (U.S. Orphan Drug Act, EU Orphan Regulation, etc.) greatly stimulated R&D for rare diseases by offering incentives. The resulting trend over the past few decades has been a steady rise in orphan drug designations and approvals:

- In the US, the FDA's Office of Orphan Products Development has granted over 6,000 orphan designations since 1983, leading to more than ~1,000 approved orphan drug products ([www.nome.bio](http://www.nome.bio)). These include drugs for rare cancers, hereditary diseases, infections, and more. Particularly in the last decade, orphan approvals have surged. Notably, in **2023**, **51%** of all new drug approvals by the FDA's Center for Drug Evaluation and Research (CDER) were for orphan-designated indications ([www.nome.bio](http://www.nome.bio)). This reflects a shift in pharmaceutical innovation: companies are increasingly focusing on rare diseases, in part because the science has advanced to allow targeting of these conditions, and in part because the incentives and premium pricing can make them financially viable.
- In Europe, orphan drug approvals also increased, though at a slower pace than the US. By early 2024, about 149 orphan medicines had been authorized in the EU (since 2000) (<sup>[16]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). The European Medicines Agency continues to grant dozens of orphan designations annually, but a persistent issue in Europe has been that not all EMA-approved orphan drugs are made available or reimbursed in all member countries (leading to inequality in access – a policy issue under review in the EU's orphan drug legislation reform plans).
- Japan and other countries also have seen orphan drugs introduced (Japan has approved over 100 orphan drugs by its PMDA since its orphan policy inception).

It's important to clarify that **"having a treatment"** might vary in meaning. Some rare diseases have treatments that address the root cause (like enzyme replacement providing the missing enzyme in Gaucher disease), while others have only symptomatic treatments (like anti-seizure drugs for seizures in a rare syndrome, but nothing that alters the disease itself). For purposes of the 5% figure, typically it refers to diseases with at least one drug approved explicitly for that disease. Many rare diseases are managed off-label by borrowing medicines approved for other conditions when possible – for instance, using chemotherapy drugs for certain rare autoimmune diseases – but those aren't counted as dedicated treatments.

**Therapeutic Modalities and Breakthroughs:** In the minority of rare diseases that do have treatments, a variety of therapeutic approaches have been employed:

- **Enzyme Replacement Therapy (ERT):** One of the earliest successes in rare diseases was enzyme replacement for certain lysosomal storage disorders. Gaucher disease (a rare metabolic disorder causing organ enlargement and bone issues) was the first to get ERT in 1991 (alglucerase, later imiglucerase). This transformed Gaucher from potentially lethal to manageable, as regular infusions of the missing enzyme greatly reduce symptoms. ERTs were subsequently developed for Fabry disease, Pompe disease, MPS I, II, VI, and others. While effective at slowing disease progression, ERTs are extremely expensive (often \$200k–\$400k per year) and require lifelong infusions. They also may not penetrate certain tissues (e.g., they often don't cross the blood-brain barrier, so neurological aspects of diseases like MPS may not be fully treated). New approaches like enzyme chaperones and substrate reduction therapy have also been used for some of these conditions.
- **Small Molecule Drugs:** Small molecule pills have been game-changers for some rare diseases. A marquee example is **ivacaftor (Kalydeco)**, approved in 2012 as the first drug to address the underlying defect in

cystic fibrosis (CF). CF is caused by mutations in the CFTR ion channel; ivacaftor fixes the channel's gating defect for a particular mutation, dramatically improving lung function in those patients

[<https://www.nejm.org/doi/full/10.1056/NEJMoa1105185>]. This was followed by combination modulators (e.g., the triple therapy elxacaftor/tezacaftor/ivacaftor, brand Trikafta/Kaftrio) that benefit ~90% of CF patients. These modulators have essentially altered CF from a fatal disease in early adulthood to a chronic condition where patients might live into old age (<sup>[8]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)) (<sup>[29]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)).

Other examples of small molecules: **ataluren** (Translarna) for nonsense-mutation Duchenne muscular dystrophy (its efficacy is debated, but it aimed to allow read-through of premature stop codons); **miglustat** for Gaucher type 1 (substrate reduction); and **sirolimus** (an mTOR inhibitor) repurposed for the rare vascular disorder lymphangioleiomyomatosis (LAM), which stabilizes lung function [<https://pubmed.ncbi.nlm.nih.gov/20573880/>].

- Biologics (Monoclonal Antibodies and Others):** Monoclonal antibodies have been employed for some rare diseases, especially in immunology. For example, **eculizumab (Soliris)** is a monoclonal antibody that inhibits complement protein C5 and is used for several ultra-rare conditions like paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic-uremic syndrome. It has literally life-saving effects (preventing hemolysis and blood clots in PNH patients), but at a cost of ~\$500,000 per year or more (<sup>[30]</sup> [chrncle.com](https://www.chrncl.com)). Soliris was once cited as the world's most expensive drug annually until even pricier gene therapies arrived. Its successor **ravulizumab (Ultomiris)**, a longer-acting C5 inhibitor, is similarly costly (<sup>[31]</sup> [chrncle.com](https://www.chrncl.com)). Monoclonals are also used in some rare autoimmune or inflammatory diseases – for example, **canakinumab** for periodic fever syndromes, or **elotuzumab** for a rare type of multiple myeloma.
- Gene Therapy:** Perhaps the most exciting wave in rare disease therapeutics has been gene therapy – delivering a correct copy of a gene to patients who have a defective one. After decades of research and early setbacks, the gene therapy field has matured and multiple gene therapies are now approved, nearly all for rare diseases. Some milestones:
  - Strimvelis** (2016, EU): First ex-vivo gene therapy approved, for ADA-SCID (a form of severe combined immunodeficiency). Uses patient's bone marrow cells modified with a retrovirus to add the ADA gene. It effectively cures the immune deficiency, though uptake was limited since bone marrow transplant is an alternative and Strimvelis was expensive and only available in one site in Italy initially.
  - Luxturna** (2017, US): An AAV vector delivering the RPE65 gene to retinal cells, restoring some vision in patients with RPE65 mutation-associated retinal dystrophy (Leber's congenital amaurosis). Luxturna showed significantly improved night vision and sight navigation abilities in treated patients, marking the first in vivo gene therapy approved in the US [<https://www.fda.gov/news-events/press-announcements/fda-approved-groundbreaking-gene-therapy-treat-rare-form-blindness>].
  - Zolgensma** (2019, US): An AAV9 gene therapy for Spinal Muscular Atrophy Type 1, delivering the SMN1 gene. In clinical trials, a one-time infusion of Zolgensma saved infants from death or permanent ventilation and allowed many to achieve motor milestones like sitting and even walking [<https://www.nejm.org/doi/full/10.1056/NEJMoa1706198>]. Dubbed a "cure" by some (though long-term outcomes are still being studied), Zolgensma famously was priced at \$2.1 million for a single dose—at the time, the most expensive drug ever (<sup>[32]</sup> [chrncle.com](https://www.chrncl.com)) (<sup>[33]</sup> [chrncle.com](https://www.chrncl.com)). Despite the price, its cost-effectiveness has been debated given the severe outcome of untreated SMA, and insurers have by and large covered it with outcomes-based agreements.
  - Gene Therapies for Blood Disorders:** In 2022, betibeglogene autotemcel (*Zynteglo*) was approved in the US for beta-thalassemia, allowing patients to become transfusion-independent. The price tag was ~\$2.8 million (<sup>[34]</sup> [chrncle.com](https://www.chrncl.com)). Another gene therapy, *Skysona* for the rare cerebral adrenoleukodystrophy, was approved in EU and US (priced around \$3 million) (<sup>[35]</sup> [chrncle.com](https://www.chrncl.com)). Most recently, *Elevidys* (delandistrogene moxeparovec) was FDA-approved in 2023 as the first gene therapy for Duchenne muscular dystrophy, at an initial price of \$3.2 million ([chrncle.com](https://www.chrncl.com)). And in late 2022, *Hemgenix* was approved for hemophilia B at

\$3.5 million (<sup>[37]</sup> chrncle.com), which was overtaken in 2023 by *Libmeldy* (gene therapy for metachromatic leukodystrophy) at \$4.25 million as the world's most expensive drug (<sup>[38]</sup> chrncle.com).

- These gene therapies represent something revolutionary: one-time treatments aimed at **curing** or substantially ameliorating diseases that otherwise require lifelong supportive care. The up-front costs are extremely high, but if they indeed provide lifetime benefit, they might be cost-effective over the long term. However, questions remain about durability of effect (some gene therapies might wane in efficacy after years) and about how to ensure patient access given budget impacts.
- **RNA Therapies:** Another modality making headway in rare diseases is RNA-targeted therapy, including **antisense oligonucleotides (ASOs)** and **siRNA (small interfering RNA)**. ASOs are short DNA/RNA molecules that can modulate splicing or silence a gene. A landmark example is **nusinersen (Spinraza)**, an antisense drug for spinal muscular atrophy (SMA) that alters splicing of the SMN2 gene to produce more functional SMN protein. Approved in 2016, Spinraza was the first treatment for SMA and dramatically improved survival and motor function in infants when given early (<sup>[39]</sup> investors.biogen.com) (<sup>[40]</sup> investors.biogen.com). It requires intrathecal (spinal) injections every 4 months for life, and costs ~\$750,000 in the first year and ~\$375,000 annually thereafter (<sup>[41]</sup> chrncle.com). Despite the burden and cost, it has become standard of care for SMA globally wherever available, and it set the stage for gene therapy and oral small-molecule (risdiplam) that followed for SMA.
- Other ASOs include **eteplirsen, golodirsen, viltolarsen** (exon-skipping ASOs for certain subtypes of Duchenne MD, enabling production of a truncated but partially functional dystrophin protein; these have been conditional approvals with debated efficacy but offer some hope for slowing DMD).
- **Milasen** is the famous n=1 ASO created for a single patient (Mila) with Batten disease – not a commercial product but proof that bespoke ASOs can be made in under a year to match an individual's mutation (<sup>[42]</sup> chrncle.com).
- **Small interfering RNAs (siRNA):** These have come to market for a couple of rare diseases. The first was **patisiran (Onpattro)** in 2018 for hereditary transthyretin amyloidosis, which silences the mutant TTR protein production, halting progression of this fatal neuropathy [<https://www.nejm.org/doi/full/10.1056/NEJMoa1716153>]. Another siRNA, **givosiran**, treats acute hepatic porphyria by silencing an enzyme to reduce toxic metabolite buildup.
- **Repurposed Drugs:** In some cases, drugs developed for common conditions have found use in rare diseases after serendipitous discovery or research. For example, **beta blockers** (like propranolol) turned out to be a therapy for infantile hemangiomas (a rare vascular tumor in infants). Low-dose **arginine** (a common amino acid supplement) is life-saving in the ultra-rare metabolic crisis caused by urea cycle disorders (like OTC deficiency). While repurposing doesn't get as much fanfare as novel drugs, it's an important part of rare disease therapeutics – often providing accessible, cheaper interventions. An example from the COVID-19 pandemic: the steroid **dexamethasone** improved survival in severe COVID; dexamethasone has long been used in certain rare disorders like Duchenne muscular dystrophy to prolong ambulation, illustrating how drugs can cross between rare and common usage.

**Challenges in Orphan Drug Development:** Why do 95% of rare diseases remain without treatments despite the scientific advances and incentives? Key challenges include:

- **Scientific Knowledge Gaps:** Many rare diseases are not fully understood in terms of pathology or key molecular targets. It's hard to design a therapy if the disease mechanism is unclear. For thousands of rare diseases, we might know the gene but not how the mutation causes symptoms, or we might not have good laboratory models (animal or cellular) to test potential treatments. The International Rare Diseases Research Consortium (IRDIRC) and others stress the need for basic research to unravel disease mechanisms as a predicate to therapy development.
- **Tiny Patient Populations:** Conducting clinical trials is inherently difficult when only a few hundred or fewer patients exist worldwide, and they are geographically dispersed. Traditional randomized trials may be

unfeasible. For instance, in an ultra-rare disease with 20 known patients, one cannot run a conventional placebo-controlled trial. Regulators have shown flexibility – accepting single-arm trials with historical controls, or using biomarkers as endpoints – but establishing safety and efficacy with statistical confidence is still a hurdle. Moreover, recruiting even those few patients can be logistically challenging; travel may be needed to a central trial site, etc. Trials for rare pediatric diseases are especially delicate due to ethical and practical issues in involving children.

- **High R&D Costs vs. Market Size:** Developing any new drug costs on the order of hundreds of millions of dollars on average. For a rare disease that might have only 1,000 patients, recouping that investment is difficult unless the drug is priced extremely high. This economic reality is why orphan drugs often have staggeringly high prices. Companies set prices to recover costs and make a profit from a small sales volume. While incentives (tax credits, market exclusivity) help, they don't eliminate development costs. Some ultra-rare diseases are so small in population that even a high price might not be enough to attract a commercial developer. This is referred to as the "n=1 problem" – in the extreme, diseases affecting single-digit patient numbers rely on academic or philanthropic efforts, since a traditional business model fails. Non-profit foundations or government grants often step in to support research for these diseases.
- **Regulatory and Trial Design Hurdles:** Regulators like FDA and EMA have pathways for orphan drugs, but still, demonstrating safety and effectiveness is mandatory. With few patients, trials might rely on surrogate endpoints or shorter durations, which can leave some uncertainty. There have been instances where drugs looked promising in small uncontrolled studies but failed when tried in a slightly larger cohort. Rare disease heterogeneity can be an issue too – some conditions have various subtypes, and a therapy might only work for a subset (e.g., a gene therapy targeting one genetic mutation won't help patients who have a different mutation). Deciding on appropriate endpoints (clinical outcome vs. biomarker) and overcoming placebo effect concerns (especially in subjective endpoints like pain or fatigue) are active topics of discussion in orphan drug clinical trial methodology (<sup>[43]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)).
- **Manufacturing and Delivery:** Some novel therapies (gene and cell therapies) are complex to manufacture and deliver. Scaling up production for even a small patient group can be challenging, as seen with personalized therapies. In cases like CAR-T cell treatments for rare cancers or ex vivo gene therapies, each patient's product is essentially custom-made, requiring specialized facilities. Ensuring quality and consistency, and doing so cost-effectively, is an ongoing challenge.

**Trends and Strategies in Development:** Despite these challenges, there are strategies being deployed to accelerate rare disease therapy development:

- **Platform Technologies:** A notable trend is adopting platform approaches where one technological solution can be adapted to multiple rare diseases. For example, AAV gene therapy vectors – once a particular vector system is proven safe, it can be retargeted with different genes for different diseases somewhat modularly. Similarly, antisense oligonucleotides can be rapidly designed for different target RNAs. Companies and research consortia are working on libraries of vectors or ASOs to enable faster turnaround for new diseases. The U.S. NIH's **Bespoke Gene Therapy Consortium** (BGTC) launched in 2021 aims to create standardized gene therapy delivery methods that could be customized for dozens of different rare diseases more easily [[https://commonfund.nih.gov/sites/default/files/CF Gene Therapy Factsheet.pdf](https://commonfund.nih.gov/sites/default/files/CF_Gene_Therapy_Factsheet.pdf)]. The n-Lorem Foundation is pursuing a similar concept but for antisense drugs for ultra-rare mutations, providing them free to patients under research protocols.
- **Adaptive Trial Designs and Data Sharing:** Innovative trial designs like basket trials or platform trials allow testing a therapy in multiple small patient cohorts simultaneously or sequentially. N-of-1 trials (single patient trials) with sophisticated statistics can sometimes demonstrate a drug's effect in an ultra-rare disease by using each patient as their own control (for example, comparing pre- and post-treatment disease trajectory). Regulators have shown willingness to consider evidence from observational data, patient registries, and natural history studies to augment clinical trial data. Natural history data (how the disease progresses untreated) is crucial in rare diseases – it can serve as a comparator when a placebo group is

unethical or not feasible. Many patient organizations now sponsor longitudinal studies of their disease to create a solid baseline for future trials.

- **Collaboration and Crowdsourcing:** Pharma companies, academic researchers, and patient groups often collaborate in pre-competitive alliances, sharing data and compound libraries to target rare diseases. The Cystic Fibrosis Foundation's venture philanthropy model is a famous example: the foundation invested in early research and partnered with pharma (Vertex) to develop CFTR modulators, reaping a return that they then reinvested in further research – a model now emulated by other disease groups. Crowdsourcing has also been attempted, exemplified by platforms like FixRare (which list rare disease research challenges to attract scientists) and InnoCentive challenges posed by foundations to solve a specific problem for a reward.
- **Global Market and Patient Advocacy Pressure:** Orphan drugs, despite small per-disease markets, collectively have become a lucrative sector. Global orphan drug sales were estimated at \$216 billion in 2025 and projected to grow substantially [<https://www.globenewswire.com/news-release/2023/10/17/2761771/0/en/Orphan-Drug-Market-to-Reach-USD-621-85-Billion-by-2034-Driven-by-Rising-Rare-Disease-Incidence-and-Innovation.html>]. This growth draws more biotech startups into the field. Additionally, strong advocacy has led to special regulatory designations like *Breakthrough Therapy* or *Accelerated Approval* for rare disease drugs, expediting their development and review. More than 60% of orphan drugs receive some form of expedited review or assistance from FDA (Fast Track, Priority Review, Accelerated Approval) ([www.nome.bio](http://www.nome.bio)).
- **Ethical Frameworks:** There is an increasing ethical push to ensure rare disease patients are given opportunities to try experimental therapies when no alternatives exist (expanded access or compassionate use programs). This can sometimes generate anecdotal evidence that guides therapy development. However, it's a double-edged sword; broad compassionate use can undermine trial recruitment. The balance is delicate, and regulators/pharma often get criticized in these scenarios. The 2018 "Right to Try" legislation in the US, for instance, sought to give patients access to investigational drugs outside of trials, though uptake has been limited.

**Cost and Access Considerations:** It's impossible to discuss orphan drug therapeutics without touching on their cost. Nearly all new rare disease treatments come with very high prices, often hundreds of thousands of dollars per year or, for one-time therapies, seven-figure sums (<sup>[38]</sup> [chrncle.com](http://chrncle.com)) (<sup>[32]</sup> [chrncle.com](http://chrncle.com)). For example, **Libmeldy** gene therapy ~\$4.25 million (<sup>[38]</sup> [chrncle.com](http://chrncle.com)); **Zolgensma** \$2.1 million (<sup>[33]</sup> [chrncle.com](http://chrncle.com)); enzyme therapies often \$200k–\$300k/year; even small molecules like CFTR modulators cost ~\$300k/year per patient. These prices strain healthcare payers and lead to difficult questions: Can health systems afford to pay millions per patient? Are these prices justified by the R&D cost and value delivered? There have been cases where insurers or national health services initially refused to cover a drug due to cost (for instance, some countries delayed covering Spinraza for SMA until price negotiations or coverage criteria were established). Over time, managed entry agreements – such as paying for performance (only paying fully if the drug works as expected) or installment plans for gene therapies – have emerged to mitigate the budget impact (<sup>[44]</sup> [chrncle.com](http://chrncle.com)) (<sup>[45]</sup> [chrncle.com](http://chrncle.com)). Outcomes-based reimbursement is increasingly used: e.g., if a child treated with a gene therapy doesn't achieve certain milestones, the payer may get a refund or discount. These models are still evolving. Nonetheless, in high-income countries, there is usually some path to access via insurance or government coverage, albeit after negotiation and sometimes with restrictions.

In lower-income countries, the situation is far more dire: most orphan drugs are simply unaffordable and not reimbursed. This creates a "treatment divide" – a child with SMA in a country with advanced healthcare might get a \$2 million gene therapy paid by insurance, whereas in a poorer country, that therapy is out of reach and the child will succumb. Humanitarian programs by companies (donation programs) exist for a few drugs, but they cover only a sliver of need. The WHO's rare disease resolution in 2025 emphasizes improving affordability and accessibility globally (<sup>[25]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)), but it will require substantial effort and innovative financing to bridge this gap.

**Notable Success Stories:** It is worth highlighting a few rare disease treatment success stories that exemplify what is possible:

- *Spinal Muscular Atrophy (SMA)*: As mentioned, from 0 treatments before 2016 to three treatments by 2020 (Spinraza, Zolgensma, and risdiplam). The combination of newborn screening + early treatment has virtually eliminated SMA type 1 deaths in places like the US where this approach is implemented. Children who would have died as infants are now walking and attending school (<sup>[39]</sup> [investors.biogen.com](https://investors.biogen.com)) (<sup>[40]</sup> [investors.biogen.com](https://investors.biogen.com)). SMA went from a heartbreaking untreatable disease to a neurological disease model of effective therapeutics in less than a decade.
- *Hepatitis C (a formerly rare example of curative treatment)*: Although not rare, the paradigm of curing a viral disease with drugs (DAAs for Hep C) influenced thinking in rare diseases – showing that with focused effort, even seemingly intractable chronic conditions can be cured.
- *Paroxysmal Nocturnal Hemoglobinuria (PNH)*: Before eculizumab, many PNH patients died of thrombosis or lived with debilitating transfusion-dependent anemia. Eculizumab normalized life expectancy for many and turned PNH into a controlled chronic condition. It's a triumph of understanding complement biology and applying a targeted therapy.
- *Hereditary ATTR Amyloidosis*: A deadly neuropathic disease now has both an ASO (inotersen) and siRNA (patisiran) that halt progression, and even a stabilizer drug (tafamidis) for cardiomyopathy. This disease was usually fatal within a decade of symptom onset; we now see patients stabilized or only mildly progressing.
- *Leukocyte adhesion deficiency type I (LAD-I)*: An ultra-rare immunodeficiency that recently saw a gene therapy cure in clinical trials (the gene therapy, called *Strimvelis* for ADA-SCID's concept was extended to LAD-I in research, and a child who was severely ill is now healthy) [<https://www.nejm.org/doi/full/10.1056/NEJMoa2114504>].
- *Cancer Therapeutics Crossover*: Numerous targeted cancer drugs initially approved for rare molecular subtypes of tumors (hence orphan-designated) have now shown efficacy in broader contexts. Conversely, some rare disease drugs emerged from oncology – for example, sirolimus (mTOR inhibitor) was an immunosuppressant and cancer drug but then found to treat rare overgrowth syndromes (like tuberous sclerosis complex). The cross-pollination is increasingly common, blurring lines between “rare” and “common” drug development.

**Pipeline and Future Treatments:** As of 2025, the pipeline for rare disease drugs is robust. Hundreds of investigational therapies for rare conditions are in clinical trials. Gene therapies are being tested for hemophilia A (valoctocogene roxaparvovec, recently approved as Roctavian in Europe), sickle cell disease (ex vivo CRISPR and lentiviral approaches, with the first approvals expected around 2025–2026), various neuromuscular diseases (e.g., another gene therapy for DMD micro-dystrophin, gene therapy for ALS SOD1 mutation, etc.), and metabolic diseases. The first in vivo **CRISPR gene editing** therapy trial (for transthyretin amyloidosis by Intellia) showed successful gene editing in humans in 2021, offering a one-time infusion that knocked down the disease-causing protein by >90% [<https://www.nejm.org/doi/full/10.1056/NEJMoa2107454>]. This is a new approach where CRISPR is delivered via lipid nanoparticles to the liver – a potentially broad platform for many liver-mediated rare diseases.

There is also excitement around **base editing** (an advanced form of gene editing) which is being tried for certain blood disorders, and **gene silencing by RNAi** for more diseases. *Gene replacement via mRNA* (the same concept as COVID-19 vaccines but for protein deficiencies) is another area – e.g., using mRNA to transiently produce an enzyme like in propionic acidemia (Moderna has trials on this). If successful, mRNA therapy could function like an “injectable protein factory” without the need for viral vectors.

**Personalized medicine** is pushing boundaries: scientists are exploring how to create tailored genetic or molecular therapies for *each patient's unique mutation* if needed. This approach is exemplified by the n=1 trials like milasen. While not scalable with current regulatory and economic frameworks, efforts are underway to

streamline n-of-1 drug development for certain scenarios (for instance, the FDA has shown openness to personalized ASOs, and guidelines are being discussed to reduce the burden of preclinical testing when only one patient will receive the drug, under careful monitoring).

**Summary of Therapeutic Landscape:** In summary, the therapeutic landscape for rare diseases in 2025 is one of both tremendous hope and sobering gaps. On one hand, **unprecedented innovations** – gene therapy, gene editing, ASOs, enzyme replacements – are yielding dramatic successes and fundamentally changing what a diagnosis means for some patients (SMA being a prime example, turning a fatal disease into a treatable one). On the other hand, **thousands of diseases remain untouched by this progress**, and for those patients, the situation in 2025 is not much different than in 1985 – they rely on symptomatic care and the hope of research breakthroughs. The successes have shown what is possible; the task ahead is to generalize those successes across many more diseases. As one researcher put it, “We have cured rare diseases – we just haven’t cured *your* rare disease (yet).” The collective aim for the next decade is to shrink the 95% of diseases with no treatment, bridging scientific discovery to therapy more efficiently and ensuring patients worldwide can benefit from these medical advances.

Having examined the big picture of treatment development, we will now turn to more *personal perspectives* and real-world experiences. The next section will present stakeholder perspectives – from patients and families to physicians, researchers, and industry – to understand how rare diseases are experienced and tackled on the ground. This will be followed by detailed case studies highlighting specific rare disease stories of success and struggle.

## Stakeholder Perspectives in Rare Diseases

Rare diseases impact a wide array of stakeholders, each with unique concerns, challenges, and contributions. Here we explore perspectives from patients and families, healthcare providers, researchers, pharmaceutical industry, and policymakers. Understanding these viewpoints provides a holistic picture of the rare disease ecosystem and why multi-stakeholder collaboration is crucial.

### Patients and Families

For patients living with rare diseases – and their families – the experience can be harrowing and all-consuming. Patients often suffer from serious, progressive symptoms that interfere with daily life. Many rare diseases cause chronic pain, physical disability, cognitive impairment, or a combination of these. A common issue is the sense of **isolation** – patients often feel alone because they have never met another person with the same condition and the general public (and sometimes their own extended family or community) has never heard of their disease. Unlike more common diseases, there may be no local support group or even local doctor with expertise.

Parents of children with rare diseases frequently describe the emotional rollercoaster: the initial confusion and denial when their child’s development seems off, the frustration and desperation during the diagnostic odyssey, and then the complicated emotions upon diagnosis – relief at having an answer, but fear and grief if the diagnosis is severe. Day-to-day life for families can revolve around medical care tasks: managing feeding tubes or ventilators, administering multiple medications, attending therapy sessions, and dealing with medical emergencies. **Caregiver burden** is extremely high. A study in Poland found that family caregivers of rare disease patients reported significantly worse quality of life and financial well-being compared to general population, with many having to reduce work hours or quit jobs to provide care (<sup>[46]</sup> [pmc.ncbi.nlm.nih.gov](#)) (<sup>[47]</sup> [pmc.ncbi.nlm.nih.gov](#)). In the U.S., a 2019 economic burden study showed that **indirect costs** (like lost caregiver productivity) accounted for 44% of the total rare disease cost, almost equal to direct healthcare costs (<sup>[10]</sup>

ojrd.biomedcentral.com). This indicates families often lose income and incur extra non-medical expenses (travel to specialist centers, home modifications, special education, etc.).

Psychologically, patients and families deal with chronic stress and uncertainty. Progressive rare diseases can feel like a “slow ticking clock” if no treatment is available. Mental health issues such as anxiety and depression are prevalent among rare disease patients and caregivers. Yet, mental health support is often lacking or not tailored to their situation. There’s also the burden of becoming an advocate and expert. Many patients/families become quasi-specialists in their disease out of necessity – they learn to read medical literature, coordinate complex care among multiple specialists, and sometimes fight for access to off-label treatments or clinical trials. The phrase “parents as the CEO of their child’s illness” is apt in rare diseases.

On a positive note, the rare disease patient community often finds resilience and empowerment through **advocacy and networking**. With the advent of social media and patient registries, even if there are only 50 people in the world with a condition, they can form a group online. These networks provide emotional support and practical tips. Patients swap advice on managing symptoms, navigating insurance, or pursuing research. Many rare disease foundations were started by parents or patients who wanted to create the support they lacked. For instance, the **Progeria Research Foundation** was founded by parents of a child with progeria and has driven research leading to the first clinical trial and treatment (<sup>[48]</sup> [www.prnewswire.com](http://www.prnewswire.com)) (<sup>[49]</sup> [www.biospace.com](http://www.biospace.com)). Similar stories exist for numerous disorders (Cystic Fibrosis Foundation by parents in 1955, FRAXA for fragile X syndrome by parents in 1994, etc.).

Patients also bring a **sense of urgency** that fuels progress. Their voices have been critical in shaping policy – e.g., patient advocacy was instrumental in passing the Orphan Drug Act, establishing rare disease advisory committees, and demanding faster regulatory approvals for serious conditions. “Nothing about us without us” is a mantra, meaning patients want to be involved in decisions around research and policy.

## Healthcare Providers

From the perspective of healthcare providers (HCPs) – doctors, nurses, genetic counselors, etc. – rare diseases present both challenges and opportunities. For general practitioners and community clinicians, a key issue is **limited knowledge**. With thousands of rare diseases, it’s impossible for any single provider to know them all. Medical training historically has not emphasized rare diseases beyond a few illustrative cases. Many physicians report feeling ill-equipped to suspect or manage rare diseases. For example, a survey in the Kingdom of Bahrain showed that while most healthcare professionals had heard of common rare diseases like thalassemia, their overall knowledge of rare diseases was suboptimal and they desired more education on the topic (<sup>[50]</sup> [pmc.ncbi.nlm.nih.gov](http://pmc.ncbi.nlm.nih.gov)).

Clinicians can experience frustration when dealing with an undiagnosed complex patient – they want to help, but without awareness or resources, they might be at a loss. Some might even dismiss patients’ symptoms (as psychosomatic or exaggerated) if they can’t find an explanation, which contributes to patient frustration. There is also an emotional toll: pediatricians have recounted the difficulty of telling parents that their child has a lethal rare disease with no cure, or conversely, the helpless feeling of witnessing a patient deteriorate while waiting for a clinical trial or drug approval.

However, for medical specialists, rare diseases can be intellectually rewarding and motivating. Many geneticists, metabolic specialists, and academic physicians choose to focus on rare diseases precisely because each case is a complex puzzle. Successfully diagnosing a rare condition can be a career highlight, and treating these patients, while challenging, is often deeply meaningful – these doctors often form long-term bonds with families as they guide them through the journey. There are stories of clinicians going above and beyond: spending nights poring over literature to find a clue for a patient’s condition, or collaborating internationally to find similar cases.

The diagnostic triumphs, such as identifying a novel disease gene explaining a patient's illness, are rewarding academically and personally.

Healthcare providers also face **systemic hurdles**: coordinating care for rare disease patients is complicated. Often a multidisciplinary approach is needed – for instance, a child with a complex syndrome might need a pediatrician, neurologist, cardiologist, physical therapist, nutritionist, etc. Ensuring all these providers communicate and align can be difficult, especially if there's no dedicated case manager. Many countries have few specialized centers for specific rare diseases, so providers must refer patients to out-of-region experts, dealing with referral barriers or insurance issues.

Additionally, administering new therapies like gene or enzyme treatments requires special training and infrastructure. A local hospital might not have experience handling an infusion for a lysosomal disease or monitoring gene therapy side effects, so providers must quickly learn and adopt new protocols as orphan drugs emerge. Some HCPs fear the medico-legal risks because rare disease treatments are so novel and high-stakes – they want to ensure patient safety while navigating unfamiliar territory.

Encouragingly, networks like the **European Reference Networks (ERNs)** and similar concepts elsewhere are helping providers by offering access to pooled expertise. A doctor in a small town can virtually consult a panel of rare disease experts via telemedicine. Genetic counselors have also become key players – they help interpret genetic test results and counsel families on recurrence risks and family planning, an essential service given many rare diseases are inherited.

In summary, clinicians view rare diseases as an area where lifelong learning is required. There's a need for better integration of rare diseases into medical education and continuing training. Many providers express that they gain a great sense of purpose by making a positive impact on a rare disease patient's life, but they need more support, resources, and recognition for the complexity involved.

## Researchers and Scientists

For biomedical researchers, rare diseases can be both a challenge and a font of discovery. Scientifically, each rare disease is a window into human biology – it's often said that rare diseases are "experiments of nature" that can reveal fundamental mechanisms. Indeed, studying rare genetic disorders has led to insights far beyond the specific disease. For example, research on familial hypercholesterolemia (a rare cholesterol disorder) paved the way for statin drugs that help millions of people with common cardiovascular disease. The discovery of the PCSK9 gene through a rare familial cholesterol condition led to PCSK9 inhibitors for cholesterol control [<https://www.nejm.org/doi/full/10.1056/NEJMp058171>]. Similarly, studying rare familial cancers with specific mutations guided development of targeted cancer therapies.

Researchers often find rare disease work rewarding because the patient communities are motivated and engaged. Unlike some common disease research that can feel abstract, rare disease researchers frequently interact with patient organizations, attend family conferences, and see directly who their work may benefit. This personal connection can be a powerful motivator. It's not uncommon for scientists to become deeply passionate advocates for the disease they study.

However, there are pragmatic difficulties. **Funding** is a perennial issue. Rare disease research historically received less funding than research on prevalent diseases. It can be harder to attract grants, although this is gradually changing as rare diseases gain attention. The NIH and EU funding bodies have special programs for rare diseases, but competition remains stiff. Private foundations (often started by families) play a surprisingly large role in funding early-stage rare disease research. There are stories of small foundations raising funds through bake sales and marathons to support a postdoc's salary in a lab investigating "their" disease. For instance, the FOXG1 Research Foundation (for a rare neurodevelopmental disorder) or the A-T Children's Project (ataxia-telangiectasia) have funded basic research that later led to larger grants or industry interest.

Another challenge for researchers is access to **models and data**. Animal models (mice, zebrafish, etc.) might not exist for an ultrarare disease, so creating a model (transgenic mouse with the patient's mutation) is an expensive upfront need. Cell lines from patients or induced pluripotent stem cells (iPSC) are increasingly used to model diseases in a dish, but obtaining patient samples requires collaboration with clinicians and patients. Biobanks and patient registries are invaluable to researchers because they provide biological samples and natural history data for analysis. Fortunately, many patient groups actively facilitate this, organizing registries and encouraging patients to donate samples for research.

In academic career terms, focusing on a very rare disease can be seen as risky. Young researchers might worry that working on a condition affecting 100 people may not lead to high-profile publications or stable funding. This is a valid concern as academia often rewards breadth and impact. But there's a trend towards valuing rare disease research more, especially as those projects do often yield novel biology or cross-over insights (and journals and funding agencies are recognizing the importance of helping these neglected conditions). Some scientists also use rare disease research to carve out a unique niche, becoming the go-to expert in that domain.

**Collaboration** is a hallmark of rare disease research. Because patient numbers are small and expertise is scattered, researchers must collaborate internationally to get robust results. The rare disease research community can be quite collegial, sharing data pre-publication at conferences to advance the field collectively. There are international research consortia for various diseases (e.g., the Inherited Neuropathy Consortium for Charcot-Marie-Tooth disease, etc.). IRDiRC, mentioned earlier, coordinates at a high level to avoid duplication and promote data sharing (like encouraging common data standards so that patient registry data can be pooled).

Researchers sometimes face an emotional element too – getting to know patients can add urgency but also pressure. When a patient or parent asks a scientist “When will your research lead to a cure?” it's both inspiring and stressing. Scientists have reported that involvement with patient communities keeps them mission-focused, but also that it's heartbreaking when, despite their best work, progress is slow or a promising treatment fails. The stakes feel high because behind every experiment, they envision the patient families waiting for answers.

Finally, regulatory science is an area some researchers are engaging in – working on better trial designs and outcome measures for rare diseases (like developing a new clinical endpoint suitable for a small trial, or a surrogate biomarker that could expedite approval). This merges research with policy and is increasingly important in translating lab breakthroughs to patient treatments.

## Pharmaceutical and Biotechnology Industry

The pharmaceutical industry's perspective on rare diseases has evolved dramatically over the last few decades. Once largely avoided by big pharma, rare diseases are now seen as a viable and even attractive business segment under the right conditions. Key points from the industry viewpoint include:

- **Market Opportunity vs. Niche:** The Orphan Drug Act and global equivalents created a framework where companies could make a profit on orphan drugs despite small patient numbers. High per-patient prices and incentives offset the limited sales volume. As a result, what was once a niche philanthropy-like endeavor has become a major commercial strategy. Many big pharma companies now have dedicated rare disease units. For instance, Pfizer, Sanofi, Novartis, and others all invest in rare diseases, and some have made acquisitions of biotech specifically to build orphan portfolios (e.g., Roche acquiring Spark Therapeutics for gene therapy expertise). The rare disease drug market has experienced double-digit growth annually, outpacing growth in non-orphan drugs <sup>([\[51\]](https://www.evaluate.com) [www.evaluate.com](https://www.evaluate.com))</sup>. By 2024, orphan drugs accounted for roughly 15-16% of global pharmaceutical sales and are projected to reach ~20% by 2030 <sup>([\[6\]](https://www.dcatvci.org) [www.dcatvci.org](https://www.dcatvci.org))</sup> <sup>([\[7\]](https://www.dcatvci.org) [www.dcatvci.org](https://www.dcatvci.org))</sup>.

- **R&D Efficiency:** Some data suggest orphan drug development can have higher success rates than non-orphans. One analysis showed orphan-designated drugs have about a 25–30% likelihood of approval from Phase I, versus ~10% for non-orphans ([www.nome.bio](http://www.nome.bio)) ([www.nome.bio](http://www.nome.bio)). This is attributed partly to more targeted biology (many rare diseases are monogenic, so targeting a single known gene/protein can be more straightforward than multifactorial common diseases) and partly to regulatory flexibility in serious rare conditions (e.g., smaller trials, use of surrogate endpoints under accelerated approval). Orphan drugs also often benefit from *fast track* and *breakthrough* designations that shorten development time. A study cited by industry found that orphan drugs reach approval about 2 years faster on average than other drugs ([www.nome.bio](http://www.nome.bio)).
- **Smaller, Agile Companies:** A significant portion of orphan drug innovation comes from small and mid-size biotech companies rather than pharma giants. Between 2006–2015, 60–70% of orphan drug designations were obtained by small biotechs ([www.nome.bio](http://www.nome.bio)). These startups often form around a single disease or technology platform (for example, a gene therapy biotech focusing on a few related rare disorders). They rely on venture capital and partnership deals. Once a therapy shows promise, they might license it out or be acquired by larger companies for commercialization. The dynamic is such that big pharma often scouts the rare disease biotech space for promising candidates to bring to market (e.g., Novartis bought AveXis to get Zolgensma for SMA).
- **Pricing and Ethics:** Industry is under constant scrutiny for orphan drug pricing. Companies argue that high prices reflect the cost of research and the small patient pool. However, there have been controversies, such as companies acquiring old inexpensive drugs with small markets and then hiking prices steeply – not truly R&D-driven, but exploiting monopoly on an “orphan” product (one high-profile case: Marathon Pharmaceuticals raising the price of deflazacort, a corticosteroid for Duchenne MD). Such cases led to calls for reform, and indeed the U.S. Orphan Drug Act has been amended at times to close loopholes (e.g., to prevent granting orphan incentives for drugs that were already profitable or to stop “salami slicing” common diseases into subgroups to qualify as orphans).
- Most companies, however, know that egregious pricing will backfire with payers. So they often engage in negotiations and patient access programs. For instance, companies might cap the cost per patient for health systems or offer free drug to uninsured patients via compassionate programs. Yet, the fundamental tension remains: orphan drug prices are extremely high, raising ethical questions about sustainability and fairness. The industry perspective is that without these prices, developing the drug in the first place would be financially impossible, and that the value to patients (life-years gained, quality of life improved) justifies the cost in many cases. Independent analyses (like those by the Institute for Clinical and Economic Review – ICER in the US) sometimes agree a price is cost-effective, but not always. For example, ICER initially said Spinraza’s price was far above traditional cost-effectiveness thresholds [[https://icer.org/wp-content/uploads/2020/10/ICER\\_SMA\\_Final\\_Report\\_110617.pdf](https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Report_110617.pdf)], which put pressure on Biogen to implement discounts or value-based arrangements.
- **Regulatory Relationship:** Orphan drug developers often work closely with regulators, since these programs may need case-by-case consideration. The FDA’s orphan drug office provides protocol assistance, and EMA similarly via its COMP. Companies appreciate the collaborative approach regulators have taken – such as accepting single-arm trials if a randomized trial is not ethical or feasible. However, companies must still meet safety requirements, which can be tricky in small populations when rare side effects might not show up until post-marketing. The industry is aware that any safety issue in a high-profile gene or cell therapy could set back the whole field’s public perception, so there is a cautious approach to ensure rigorous follow-up and risk management.
- **Manufacturing and Supply:** For industry, ensuring a reliable supply of an orphan drug world-wide can be challenging. With few manufacturing sites and sometimes novel processes (like gene therapy vector production), the supply chain might be fragile. There have been instances of shortages of rare disease drugs, which can be life-threatening for patients who rely on them. Companies have to invest in robust manufacturing processes and often scale out (duplicate) facilities even if volume isn’t high, as a hedge

against problems. Another industry consideration is **distribution**: delivering ultra-expensive therapies like gene therapies often involves certifying specialty centers, training staff, and handling complex logistics (e.g., cryoshipping patient cells for ex vivo gene therapy).

- **Emerging Business Models:** Innovative payment models are being tested – for example, annuity payments (paying for a \$2M gene therapy over 5 years in installments) or “no cure, no pay” models. Industry is open to these as they can reassure payers and maybe broaden reimbursement. Additionally, some companies are exploring gene therapies that can treat multiple diseases with one product, to maximize return (e.g., AAV vectors delivering different genes might share manufacturing platforms). There’s also a trend of **gene therapy franchises** – once a gene vector is proven for one disease, companies apply it to others in the same tissue area with perhaps fewer hurdles. The cost of goods for such therapies can be high, but companies are striving to reduce manufacturing costs which in turn could allow lower prices (or higher margins).
- **Public Perception and Corporate Social Responsibility:** Companies are aware of the narrative around “price gouging” and try to balance profit and goodwill. Many participate in **Rare Disease Day** campaigns, support patient advocacy events, and invest in early research grants or disease registries that help the field at large. This can be genuine corporate social responsibility, but it also helps build relationships and understanding of patient needs, which can be beneficial when bringing a product to that patient community.

In summary, the industry perspective is increasingly that rare diseases, while challenging, represent not only a humanitarian imperative but also a viable and important segment for innovation. Pharma executives often cite the satisfaction of delivering transformative therapies for these underserved patients as aligning scientific mission with business. The caution is to do so in a way that patients can access them and that systems can afford them, which remains a topic of ongoing dialogue between industry, payers, and society.

## Policymakers and Regulators

Finally, from the perspective of policymakers and regulators: Rare diseases present a policy challenge in healthcare planning, regulatory oversight, and research funding allocation. Policymakers have to grapple with questions of equity (rare disease patients vs. common disease patients – are resources distributed fairly?), incentive structures (how to entice companies and researchers to focus on rare conditions), and integration of rare diseases into broader health systems.

**Health Policy & Planning:** Historically, rare diseases weren’t explicitly included in national health strategies. But in the last 10-15 years, many countries have developed **National Rare Disease Plans** that lay out measures to improve rare disease care. These plans often include establishing centers of expertise, creating patient registries, improving diagnostics (like funding genetic testing or expanding newborn screening), and mechanisms for access to orphan drugs (e.g., special reimbursement funds). By 2019, at least 23 countries had some form of official rare disease policy or plan (<sup>[52]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)), including many EU countries (France was the first with a plan in 2004, now on its third iteration), Canada, Japan, etc. Policymakers see these plans as critical because rare disease needs cut across traditional disease-area silos and often slip through cracks if not specifically addressed.

One focus is **care coordination**: policymakers encourage creating one-stop clinics or virtual coordination so that patients aren’t lost navigating fragmented systems. For example, some plans fund case manager positions or rare disease “hubs” where multiple specialists come together for complex cases.

**Regulatory Role:** Regulators like FDA, EMA, Japan’s PMDA, etc., have dual roles: incentivize orphan drug development and ensure safety/efficacy of treatments. They created orphan designation processes and fee waivers to reduce the barrier for companies. They also must monitor programs to prevent misuse; for instance, ensuring a company doesn’t abuse orphan exclusivity to block competition unnecessarily (there have been

criticisms that some companies filed multiple sequential orphan designations for slightly different subgroups to extend monopolies – regulators are wary of that).

Regulators are increasingly flexible and innovative when reviewing orphan therapies:

- They often accept **surrogate endpoints** or biomarkers that are “reasonably likely to predict clinical benefit” to approve drugs under accelerated approval for serious rare illnesses. For instance, reduction in neurotoxic metabolite levels might be enough to approve a metabolic disease drug without waiting years to show clinical outcome changes.
- They allow **compassionate use / expanded access** programs alongside trials for patients in urgent need who can't enroll in trials, albeit balancing that with trial integrity.
- Post-marketing surveillance is emphasized, given small pre-approval trials; regulators may require Phase IV studies or patient registries as a condition of approval to gather long-term data.

**Budget Impact and Insurance:** Policymakers (especially in countries with national health systems) face the question: how to pay for these ultra-expensive therapies? Some European countries have special funds or risk-sharing at a national level for orphan drugs to not overburden any single hospital's budget. There's discussion of international collaboration on pricing for ultra-rare drugs – for example, small countries banding together to negotiate price or share supply for extremely rare cases. HTA (Health Technology Assessment) bodies in Europe have adapted methods for orphan drugs, sometimes using higher cost-effectiveness thresholds given the high severity and lack of alternatives. Policymakers also consider implementing price caps or alternative incentives. One idea floated has been to give a larger market reward to companies (like a transferable priority review voucher or extended patent on another drug) in exchange for pricing an orphan drug lower – a kind of prize model rather than per-unit profit model. The US already has **Priority Review Vouchers (PRVs)** for rare pediatric diseases: if a company develops a drug for a rare pediatric condition, they get a voucher to expedite any future drug review or to sell to another company [<https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/priority-review-voucher-programs>]. This incentive has driven some development, though there's debate on its use.

**Global Health Perspective:** Historically, global health initiatives ignored rare diseases, prioritizing infectious diseases and common diseases. However, with the UN and WHO actions recently, policymakers in global bodies are including rare diseases in discussions about **Universal Health Coverage (UHC)**. There is recognition that rare disease patients often experience catastrophic healthcare costs, which is a UHC concern. And ethically, leaving this population behind is against the principle of health equity. The 2021 UN Resolution on Persons with Rare Diseases explicitly ties rare diseases to human rights and the Sustainable Development Goals, urging member states to integrate rare diseases into their health agendas (<sup>[53]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)). The 2025 WHO resolution tasks the WHO with developing a Global Action Plan on rare diseases (<sup>[4]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)), akin to those that exist for HIV, TB, etc., which is groundbreaking. This plan (to be formulated) will likely provide a blueprint for countries: recommending establishing national plans where absent, strengthening international research collaboration, improving diagnostic resources worldwide, and addressing affordability of treatments possibly via pooled procurement or differential pricing.

Policymakers also engage in **ethical debates**: How to allocate limited resources between many common health needs vs. expensive rare disease treatments? This is sometimes framed as a quality-adjusted life year (QALY) problem – some health economists argue for evaluating all interventions on equal footing, which often makes orphan drugs look “not cost-effective” due to price. Others argue for a modified approach, valuing the rule of rescue (the moral imperative to save lives in immediate peril regardless of cost) or giving extra weight to the severity of the condition and lack of alternatives. Countries differ in stance; the UK's NICE, for example, has a higher threshold for very rare conditions (through its Highly Specialised Technologies program) in evaluating cost-effectiveness.

Finally, **science policy** in rare diseases includes support for research infrastructure: funding genomic databases, variant interpretation networks, or newborn screening pilots. Policymakers see that relatively modest investments here can have high impact (e.g., funding a rare disease registry might help multiple research projects). There's also the idea of international data sharing frameworks – for example, the Global Alliance for Genomics and Health (GA4GH) working on standards to share genomic data, which policymakers encourage to increase the pace of discovery.

In summary, policymakers and regulators are increasingly proactive in the rare disease arena – shifting from a passive role of reacting to therapies to a more active role in shaping an environment that fosters development and equitable access. The fact that rare diseases are now on the World Health Assembly agenda in 2025 speaks to a sea change: these conditions, once in the shadow, are being recognized as a global health priority. The true measure of policy success will be in coming years: whether these high-level resolutions translate into tangible improvements in the lives of rare disease patients around the world.

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Having examined these perspectives, it is evident that addressing rare diseases requires a concerted effort from all parties: empowered patients/families, knowledgeable and compassionate providers, dedicated researchers, responsible industry players, and supportive policymakers. Each stakeholder group brings critical elements to the table, and collaboration among them has been behind many of the successes to date (for example, the development of Spinraza for SMA involved close partnership between a biotech company, academic researchers, patient advocacy groups, and regulatory fast-tracking).

The next section will illustrate how these perspectives intersect in practice by looking at specific **case studies** – real-world examples of rare diseases that highlight the challenges discussed and the remarkable progress possible when these challenges are overcome.

## Case Studies: Rare Diseases in Focus

To ground the discussion in concrete terms, we present several case studies profiling specific rare diseases. Each case study highlights different aspects of the rare disease landscape – from diagnostic odyssey to treatment breakthrough to ongoing challenges. These examples demonstrate both the hardships faced by rare disease patients and families, and the remarkable strides that coordinated research and advocacy can achieve.

### Case Study 1: Spinal Muscular Atrophy (SMA) – From Tragedy to Triumph

**Background:** Spinal Muscular Atrophy is a genetic neuromuscular disorder characterized by degeneration of motor neurons in the spinal cord, leading to progressive muscle weakness and atrophy. It is caused by insufficient levels of the Survival Motor Neuron protein (SMN), due to mutations in the SMN1 gene. SMA has several types; Type 1 is the most severe and historically the most common genetic cause of infant mortality, with onset in infancy and life expectancy of <2 years untreated (<sup>[24]</sup> [smanewstoday.com](https://www.smanewstoday.com)). Milder types (2, 3, 4) have later onset and longer survival but still cause significant disability. SMA is inherited in an autosomal recessive manner and affects roughly 1 in 10,000 live births globally.

**Historical Situation:** For decades, there was no cure or treatment for SMA. Pediatricians could offer only supportive care (feeding tubes, ventilatory support). Parents of SMA Type 1 infants were often told their child would likely die before their second birthday and that nothing could be done. The diagnostic odyssey for SMA was not as prolonged as some diseases (the clinical signs are distinctive, and diagnosis via genetic test for SMN1 deletion became available in the 1990s), but the outcome was devastating. Advocacy organizations like

Cure SMA (US) and SMA Europe formed, raising funds for research and supporting families emotionally and with equipment, but few researchers were working on SMA initially.

**Research Breakthrough:** A key insight was the presence of a second gene, SMN2, which produces a small amount of SMN protein and could partially compensate for the mutated SMN1. Researchers proposed that increasing SMN2 gene's output might treat SMA. This led to the development of **antisense oligonucleotide (ASO) therapy**. Ionis Pharmaceuticals and Biogen collaborated to create an ASO (nusinersen) that binds to SMN2 mRNA and alters its splicing, thereby boosting production of full-length SMN protein. In parallel, Avexis (a startup) worked on delivering a functional SMN1 gene via an AAV9 viral vector as a one-time gene therapy (what became Zolgensma). And Roche collaborated with PTC Therapeutics/Novartis on a small molecule (risdiplam) that also increases SMN2 splicing efficiency.

**Diagnosis and Newborn Screening:** As these therapies showed promise in clinical trials around 2015–2016, emphasis grew on early diagnosis. Data showed that treating SMA infants *before* symptom onset yields the best outcomes (<sup>[39]</sup> [investors.biogen.com](https://investors.biogen.com)) (<sup>[40]</sup> [investors.biogen.com](https://investors.biogen.com)). This spurred the push to add SMA to newborn screening (NBS) panels. In 2018, SMA was added to the U.S. Recommended Uniform Screening Panel. Several countries, like Germany and Australia, have since included SMA in NBS. This is a prime example of diagnostics aligning with therapeutics – knowing that an effective therapy exists created urgency to identify babies at birth, since an infant diagnosed even a few weeks earlier stands to avoid irreversible motor neuron loss.

**Therapeutic Revolution:** The clinical trial results for these therapies were unprecedented:

- Nusinersen (Spinraza) trial in infants (ENDEAR study) showed motor milestone achievement in ~51% of treated infants vs 0% of controls, and dramatically improved survival (clear separation from natural history where >95% would require permanent ventilation or die by 18 months) [<https://www.nejm.org/doi/full/10.1056/NEJMoa1702752>]. In an open-label study (NURTURE) treating presymptomatic newborns, **100% of infants were alive at 4.8 years and none required permanent ventilation**, with 96% able to walk with assistance – outcomes never seen in untreated SMA (<sup>[39]</sup> [investors.biogen.com](https://investors.biogen.com)) (<sup>[40]</sup> [investors.biogen.com](https://investors.biogen.com)). This showed that early Spinraza can essentially normalize development in many cases.
- Onasemnogene abeparvovec (Zolgensma) trial (START) treated SMA Type 1 infants with a single IV infusion. Treated babies, who normally would never sit, gained motor milestones: by 20 months old, 11 of 12 treated were alive and without permanent ventilation, and many could sit unassisted and even roll or crawl (<sup>[54]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov)). Long-term follow-up now shows these children continuing to live and retaining motor function. Zolgensma was approved in 2019 as the first systemic gene therapy for a neurological disease [<https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-most-severe-form>].
- Risdiplam (Evrysdi) oral drug had positive trials (FIREFISH in Type 1 SMA infants) showing significant improvement in survival and motor function as well [<https://pubmed.ncbi.nlm.nih.gov/32997988/>]. Approved in 2020, it provided an at-home administration option.

**Impact:** The transformation in SMA outcomes has been called a watershed moment in medicine. A disease that was uniformly fatal in its most common form now has children surviving, walking, and in some cases appearing near-normal. Families who once faced hopelessness now had options. For example, a baby girl diagnosed via newborn screening with SMA can receive gene therapy at one month old and potentially never develop major symptoms – essentially a cured child in function, although continued monitoring is needed. As of 2025, many SMA Type 1 patients treated early are attending kindergarten, something unimaginable a decade prior.

From a patient perspective, these therapies were life-saving but also come with complexities: Spinraza involves lumbar punctures every few months under sedation (tough on infants), and Zolgensma can trigger immune reactions requiring high-dose steroid prophylaxis. But these are manageable compared to the disease's natural course.

The challenge now is **ensuring access**. Spinraza's price at launch (~\$125,000 per dose, \$750k first year) and Zolgensma's \$2.1M one-time cost caused concerns. However, most high-income countries have managed to fund them, sometimes after negotiation. In poorer countries, SMA treatment is not widely accessible yet. The goal is to make these advances global.

**Lessons Learned:** SMA is a case where genetics pinpointed a clear target (SMN protein), multi-pronged therapeutic strategies were applied, and patient advocacy plus industry investment turned a corner. It underscores:

- The importance of early diagnosis (via NBS) to fully leverage new therapies.
- How orphan drug incentives and scientific progress (ASOs, viral vectors) can converge rapidly (all three SMA drugs were in development roughly concurrently).
- The value of patient advocacy: SMA organizations heavily funded research and lobbied for NBS inclusion and fast regulatory approvals. Cure SMA's patient registry data helped prove how dire the natural history was, strengthening the case for approvals under expedited pathways.

SMA's success brings hope to other neurological rare diseases – it has spurred interest in gene therapy for muscular dystrophies, ASOs for other genetic neurologic disorders (like ASO now approved for Huntington's disease mutation carriers in trials, etc.). It's often cited by clinicians to hesitant families of other conditions: "Remember how SMA was hopeless and now it's treatable – we are working to do the same for your disease."

## Case Study 2: Cystic Fibrosis (CF) – A Model for Targeted Drug Development

**Background:** Cystic Fibrosis is a life-limiting genetic disease affecting multiple organs, primarily the lungs and digestive system. It is caused by mutations in the CFTR gene, leading to dysfunctional chloride ion channels on cell surfaces. This results in thick, sticky mucus secretions that cause lung infections, pancreatic enzyme insufficiency, and other complications. CF is one of the more common rare diseases in Caucasian populations (about 1 in 2,500 newborns in people of Northern European ancestry), but still considered rare in absolute numbers (~30,000 patients in the US (<sup>[14]</sup> [blogs.cdc.gov](https://blogs.cdc.gov)); ~40,000 in Europe). It is inherited autosomal recessively.

**Historical Situation:** For the majority of the 20th century, CF was untreatable beyond supportive care. Median survival in the 1960s was under 10 years. Over time, aggressive chest physiotherapy, inhaled antibiotics, and better nutrition gradually extended median survival to late 20s by the 1990s. The discovery of the CFTR gene in 1989 [<https://science.sciencemag.org/content/245/4922/1059>] was a major breakthrough, enabling genetic testing (including adding CF to newborn screening panels) and raising hopes for cures like gene therapy. Early gene therapy attempts (inhaled CFTR DNA vectors) in the 1990s failed to yield lasting benefits due to delivery inefficiencies. The focus shifted to drug therapy that could fix the defective CFTR protein function.

**Precision Medicine Approach:** About 90% of CF patients have at least one copy of the F508del mutation (a deletion of phenylalanine at position 508), causing CFTR protein misfolding and degradation. Other mutations (over 1,700 known) affect CFTR in various ways (gating defects, conductance defects, minimal expression, etc.). The idea emerged to develop small molecules that target specific mutation classes:

- **Potentiators:** drugs to improve gating function of CFTR channels that reach the cell surface.
- **Correctors:** drugs to help misfolded CFTR proteins fold correctly and traffic to the cell surface.

A collaboration between the Cystic Fibrosis Foundation and a small biotech (Vertex Pharmaceuticals) exemplified rare disease venture philanthropy. The CF Foundation invested over \$150 million of patient-raised

funds into Vertex's research efforts. This led to the discovery of **ivacaftor (VX-770)**, a potentiator targeting the G551D gating mutation (present in ~4% of CF patients). In 2012, **ivacaftor** was approved – it was the first drug that treated the underlying CFTR defect (albeit only for that subpopulation). The effects were dramatic: patients with G551D had a >10% absolute improvement in FEV1 lung function within weeks (which is huge in CF terms) and marked weight gain, reduction in pulmonary exacerbations, and improved quality of life (<sup>[55]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)). Long-term data indicate ivacaftor halts the lung function decline in these patients and they maintain good lung health years later [<https://pubmed.ncbi.nlm.nih.gov/23910943/>].

Building on that success, Vertex developed **combination therapies** to tackle the most common F508del mutation. Monotherapy with correctors like lumacaftor helped a bit, but combining a corrector and potentiator worked better. In 2015, lumacaftor/ivacaftor (Orkambi) was approved for CF homozygous for F508del, showing modest lung function improvement (~3% increase in FEV1) [<https://www.nejm.org/doi/full/10.1056/NEJMoa1409547>]. Next came tezacaftor/ivacaftor (Symdeko) with similar modest benefits but better tolerance.

The real leap was **Trikafta** (brand name in US; Kaftrio in EU) – a triple combination of elexacaftor, tezacaftor (both correctors), and ivacaftor (potentiator). Approved in 2019 for ages 12+ with at least one F508del allele (later expanded to 6+ and potentially younger soon). In trials, Trikafta improved FEV1 by ~14% and reduced pulmonary exacerbations by ~60% (<sup>[56]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)). CF patients on Trikafta commonly say they feel drastically better, coughing less, gaining weight, and living essentially normal lives. By targeting the basic defect, it has changed CF from inevitable respiratory failure to a manageable chronic illness for the vast majority of patients. Modeling studies project that if started early in life, Trikafta could raise median survival into the 70s, nearly normal lifespan (<sup>[55]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)) (<sup>[8]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)). One UK simulation even predicted a median lifespan of 80+ years if therapy begins by adolescence (<sup>[8]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)) (<sup>[9]</sup> [cysticfibrosisnewstoday.com](https://www.cysticfibrosisnewstoday.com)).

**Impact on Patients:** The introduction of CFTR modulators has been life-changing. Young adults with CF on Trikafta report being able to exercise more, hold jobs, and plan for a future (something many CF patients historically struggled to do given early mortality). Hospitalizations for exacerbations have plummeted. Some patients awaiting lung transplants improved so much on modulators that they were removed from transplant lists. Quality of life improvements are documented as significant in patient surveys [<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7373927/>]. The mental health aspect is interesting – while many celebrate the “new life” modulators give, there's also a documented phenomenon of survivors' guilt or adjusting to an unexpectedly extended life, showing psychological support is still needed.

**Limitations:** Not all CF patients can benefit. A small percentage have mutations that don't produce any CFTR protein at all (nonsense mutations, etc.), for whom modulators may not work effectively. For those, other approaches like gene therapy or mRNA therapy might be needed. Clinical trials for gene therapies delivering CFTR to lungs are reviving (using better vectors or gene editing). Another limitation is cost: Trikafta's list price is around \$311,000 per year in the US, similar in Europe although negotiated discounts exist (<sup>[57]</sup> [chrncle.com](https://www.chrncle.com)). CF is a disease where patients take these drugs for decades, so long-term cost is a concern. However, many payers have decided the cost is justified given it prevents expensive hospitalizations and transplants.

**Case Study Significance:** CF showcases the power of **precision medicine** – understanding the molecular defect and developing drugs to fix it. It also exemplifies **patient-powered research**: the CF Foundation's investment and the community's participation in trials were crucial. CF care centers had decades of data (through the CF Patient Registry) that helped demonstrate improvements.

CF also highlights the need for **multi-faceted care**: Even with modulators, patients still require some traditional care like airway clearance and infection surveillance. It's not an absolute cure, but a close step. Efforts are ongoing to find curative therapies or therapies for that last 5-10% who can't use modulators (like the nonsense mutation drug ataluren was an attempt, and there's a new readthrough agent, ELX-02, in testing).

Finally, CF is being referenced by other fields as an example: e.g., in sickle cell disease (also a single-gene disorder), there's interest in small molecules or other targeted drugs beyond just curative gene therapy. CF taught pharma that even if a disease is rare by population (~80k worldwide), developing a disease-modifying drug can be hugely impactful and financially rewarding (Trikafta is one of the top-selling drugs worldwide now, with billions in annual sales [<https://investors.vertexpharma.com/node/27901/pdf>]). This business success may encourage more rare disease drug programs.

## Case Study 3: Progeria (Hutchinson-Gilford Progeria Syndrome) – Ultra-Rare Disease, Ultra-Fast Drug Development

**Background:** Progeria is an extremely rare genetic disorder that causes accelerated aging in children. The classic form, Hutchinson-Gilford Progeria Syndrome (HGPS), is caused by a de novo dominant mutation in the LMNA gene, leading to production of a toxic protein called progerin. Children with progeria appear normal at birth but within a year start showing failure to thrive, loss of body fat and hair, skin aging, stiffness of joints, and by childhood they suffer from osteoporosis, hip dislocations, and, most critically, hardened arteries (arteriosclerosis) leading to heart disease and stroke. The average lifespan is around 14.5 years (<sup>[22]</sup> [www.biospace.com](http://www.biospace.com)), with death usually from heart attack or stroke in the teen years.

Prevalence is only about 1 in 20 million; at any given time perhaps 300–400 children worldwide have HGPS (<sup>[22]</sup> [www.biospace.com](http://www.biospace.com)). Because of its rarity, there were no dedicated treatments, and management was symptomatic (low-dose aspirin to reduce stroke risk, physical therapy for joints, etc.). The Progeria Research Foundation (PRF), founded in 1999 by the parents of a girl with progeria, became the driving force behind research, identifying the gene mutation in 2003 and then seeking treatments [<https://pubmed.ncbi.nlm.nih.gov/12881528/>].

**Research to Treatment:** By understanding the molecular cause – a mutant Lamin A protein (progerin) that damages cells – researchers identified a potential strategy. Progerin accumulates due to a farnesyl group that doesn't get removed (normally Lamin A is processed and that group is cut off, but the mutation prevents the cleavage). Thus, researchers hypothesized that **farnesyltransferase inhibitors (FTIs)**, a class of cancer drugs that prevent farnesylation of proteins, could reduce progerin's toxic buildup. A specific FTI called **lonafarnib** had been developed for cancer (unsuccessfully), but in progeria cell models it showed promise in reducing progerin accumulation and improving cell nuclear shape.

PRF coordinated a clinical trial of lonafarnib in progeria children – an extraordinary effort given the ultra rarity. They managed to enroll 28 children from 16 countries in a single-arm trial at Boston Children's Hospital in 2007. Results after 2 years showed improved weight gain, better vascular stiffness measures, and extended survival compared to untreated cohorts (<sup>[58]</sup> [pmc.ncbi.nlm.nih.gov](http://pmc.ncbi.nlm.nih.gov)) (<sup>[59]</sup> [pmc.ncbi.nlm.nih.gov](http://pmc.ncbi.nlm.nih.gov)). Continued follow-up and additional trials combining lonafarnib with other drugs (to target related processing pathways) strengthened evidence that lonafarnib was having a beneficial effect: treated children lived longer than those historically untreated (<sup>[60]</sup> [www.biospace.com](http://www.biospace.com)). In 2020, lonafarnib (brand name Zokinvy) was approved by the FDA – the **first and only treatment for progeria** [<https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-hutchinson-gilford-progeria-syndrome-and-some-progeroid-laminopathies>]. Data showed it reduced the risk of death by 60% and extended average survival by about 2.5 years (<sup>[60]</sup> [www.biospace.com](http://www.biospace.com)). While not a cure, this is meaningful time for children who typically might only live to early teens (<sup>[60]</sup> [www.biospace.com](http://www.biospace.com)).

**Impact on Patients:** After approval, PRF reported that as of 2022, some children on lonafarnib were living into their late teens or 20s – some of the longest-lived progeria patients on record. The drug is an oral medication given twice daily. It has side effects (mostly gastrointestinal like diarrhea, as well as fatigue) that need

management, but families have overwhelmingly opted for treatment given the stakes. Zokinvy's approval also covers certain progeroid laminopathies (related rare mutations) which have similar pathology.

One tangible impact: before lonafarnib, very few children with progeria survived long enough to attend high school. Now, more are reaching that age. However, they still face challenges: lonafarnib doesn't reverse existing damage; children still have short stature, joint issues, and need careful cardiac monitoring. It's a first step. Researchers are exploring additional therapies: one approach is a combination of lonafarnib with a statin and bisphosphonate (tested in a trial but results weren't markedly better, however). Gene therapy is theoretically possible (to introduce a corrected Lamin A or silence progerin), but delivering gene therapy to every cell in the body (especially to blood vessels) is a hurdle. Another idea is using CRISPR to cut out the progeria mutation; in 2021, a proof-of-concept CRISPR base editing study in progeria mice extended their lifespan significantly [<https://pubmed.ncbi.nlm.nih.gov/33524990/>]. This is far from human application but offers hope for a future curative approach.

This case study is remarkable for the **speed and focus**: from gene discovery (2003) to drug approval (2020) in 17 years, which for an ultra-rare disease is quite fast, and it was largely driven by a family-founded foundation aligning scientists, drug companies (using an abandoned drug), and obtaining regulatory buy-in with small but well-designed trials. The use of a repurposed cancer drug underscores the value of looking at existing compounds for rare diseases.

Progeria's story also has outsized symbolic impact. It drew public attention (progeria kids have been featured in documentaries and media, increasing awareness of rare diseases generally). It's a striking example of translating knowledge about a rare mechanism of disease (progerin accumulation) into a treatment in a short time, relative to the norm. It exemplifies how even ultra-rare diseases benefit from the general advancement of science (FTIs from oncology being repurposed) and how patient advocacy can rally international collaboration (coordinating patients from 16 countries to a single trial is no small feat).

## Case Study 4: N-of-1 Medicine – Mila's Story (Personalized Antisense for Batten Disease)

**Background:** In late 2017, a six-year-old girl named Mila Makovec, who had a rare form of Batten disease (CLN7 variant) – a fatal neurodegenerative disorder – made headlines as the first person to receive a custom "N-of-1" experimental drug tailored just for her. Mila's case highlights the potential of individualized genetic medicine and the new ethical and regulatory frontier it represents.

Mila had been healthy until age 3, when she began to have vision problems and neurological regression. After a long diagnostic odyssey, she was found to have Batten disease CLN7, caused by biallelic mutations in the MFSD8 gene – one allele had a known mutation, while the other had a novel retrotransposon insertion that standard genetic tests initially missed (<sup>[28]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)). By age 6, Mila was blind, having frequent seizures, and losing the ability to walk or talk. Batten CLN7 usually leads to death in late childhood; there was no treatment.

**Personalized Drug Development:** Mila's mother, Julia, refused to accept that nothing could be done. She found a researcher at Boston Children's Hospital (Dr. Timothy Yu) who had experience with genomics. Dr. Yu's team identified Mila's unique mutation – a piece of "junk" DNA inserted that disrupted splicing of the MFSD8 gene. They realized an antisense oligonucleotide might mask the aberrant splice site and restore normal gene reading. In an unprecedented sprint, they designed and tested multiple ASOs in Mila's cells in the lab, identified a lead candidate that worked to reduce the mutant mRNA, and after just months of development, obtained FDA clearance to treat Mila under a compassionate use/expanded access protocol (<sup>[61]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)).

The drug, named “milasen” after Mila, was a custom 22-base ASO. In early 2018, Mila received her first dose intrathecally. Over the next year, her seizures significantly reduced in frequency and duration (~80-90% reduction in seizure burden) and the progression of her neurological decline appeared to slow (<sup>[61]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)). While milasen was not a cure – Mila’s disease had already advanced – her quality of life improved by some reports (less pain, more interaction). Mila lived for two more years, passing away at age 8 in 2021, which was longer than expected without intervention.

**Implications:** Mila’s case proved that, technically, one can go from a single patient’s genome to a tailored drug in about one year (<sup>[26]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)). This paradigm-shifting concept suggests that for some rare diseases – especially ones caused by unique private mutations in otherwise known disease genes – personalized ASOs could be crafted. Following Mila’s case, FDA has shown openness to this model, issuing draft guidance in 2021 on N-of-1 trial development [<https://www.fda.gov/drugs/news-events-human-drugs/complex-innovative-designs-n-1-trials-rare-diseases>].

Several other children have since received individualized ASOs (often referred to as “N=1 trials” or “custom therapeutics”). For instance, a boy with CLN7 from another family was given a variant of milasen tuned to his mutation. Another example: a personalized ASO was made for a girl with a rare GRIN2B mutation causing movement disorder (this ASO is called “viversen”). The n-Lorem Foundation was established to provide a non-profit route to develop ASOs for ultra-rare mutations for free.

**Challenges:** Personalized therapies face numerous challenges. Each one is essentially a new drug – requiring manufacturing, safety testing (usually minimal toxicology in an animal model if time permits), and a custom treatment plan. The cost for milasen’s development was around \$1-2 million – paid through fundraising and philanthropy [<https://www.nejm.org/doi/full/10.1056/NEJMoa1813279>]. This is relatively low for drug development, but still steep if one imagines thousands of such personal drugs. Scaling regulatory oversight is also an issue: the FDA accommodated milasen as a one-off, but if many such requests come, they need a framework. They have been working on guidelines to streamline chemistry and safety requirements for ASOs that are similar in platform but different in sequence for each patient. Ethical considerations abound: how to decide who gets a custom drug? Only those who can fundraise? Those with the fastest progressive diseases? It raises equity issues.

Nonetheless, Mila’s story has inspired a “bespoke” therapeutics movement. It suggests that, in some cases, we might not need to wait years for a commercial drug if a tailored remedy can be crafted from existing technology. It leverages the fact that antisense oligos can be designed and synthesized quickly once you know what sequence to target. As genomic sequencing becomes more common, we will identify more patients with “untreatable” mutations – Mila’s case lights a possible path to treatability.

The case study underscores the role of parent advocacy and partnership with researchers. Julia’s relentless pursuit and Dr. Yu’s team’s dedication combined to make what was essentially a laboratory experiment into a clinical reality in record time (<sup>[26]</sup> [pmc.ncbi.nlm.nih.gov](https://pubmed.ncbi.nlm.nih.gov/)). It’s a modern example of patient-centric innovation, and it has pushed regulators, researchers, and industry to think outside the conventional drug development box. If frameworks solidify, N-of-1 therapies could become a new pillar of rare disease medicine, particularly for those ultra-rare “mutations of one” that would never attract traditional R&D.

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These case studies – SMA, CF, Progeria, and Mila’s N-of-1 – each illustrate different takeaways:

- **SMA:** Importance of newborn diagnosis and the power of multiple therapeutic approaches (ASO, gene therapy, small molecule) yielding transformative results.
- **CF:** The long-game of targeted drug development with sustained advocacy, culminating in near disease-modification for most patients.
- **Progeria:** Even ultra-rare diseases can get treatments through focused research and repurposing existing drugs, extending lives and offering hope.

- **Personalized ASO (Mila):** A glimpse at a future where individualized genomics and therapy converge, raising both hope for tailored cures and questions of implementation.

Collectively, they show how progress in rare diseases is often **non-linear** – years of little advancement followed by rapid breakthroughs – and how crucial the roles of advocacy, innovative science, regulatory flexibility, and sometimes just creative problem-solving are in changing what it means to live with a rare disease.

In the final sections, we will discuss the broader implications of such advances, the current challenges that remain unaddressed, and the outlook for the future of rare disease research, policy, and care.

## Economic and Societal Impacts of Rare Diseases

Rare diseases have profound economic and societal implications that extend beyond the individuals directly affected. These impacts are often underappreciated because rare diseases, taken individually, affect relatively few people. However, collectively and cumulatively over time, they impose significant costs on healthcare systems, economies, and communities, as well as on intangible social factors like inclusion and psychological burden.

### Economic Burden

**Direct Medical Costs:** Rare disease patients often require intensive medical care, specialist consultations, frequent hospitalizations, surgeries, and long-term medications or medical devices. A comprehensive study of 379 rare diseases in the United States found that the direct medical costs (hospital care, physician services, medications, etc.) for these conditions amounted to **\$449 billion** in 2019 (<sup>[10]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)) (<sup>[11]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)). This represented about 45% of the total economic burden of those diseases, indicating that direct healthcare expenditures are substantial – nearly half a trillion dollars for just a few hundred rare diseases in one country (<sup>[20]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)) (<sup>[18]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)). To put this in perspective, this number rivals or exceeds the direct costs of more prevalent diseases like diabetes or cardiovascular diseases individually. When extrapolated to the thousands of rare diseases globally, the aggregate direct medical cost is enormous.

What drives these high costs? Several factors:

- **Diagnostic Testing:** As discussed, many rare diseases require specialized genetic or biochemical tests. These can be expensive – whole exome or genome sequencing has come down in price, but additional analyses, metabolic tests, muscle biopsies, etc., add up. Prior to diagnosis, patients often undergo numerous unnecessary tests and procedures (like multiple MRIs, invasive biopsies, or even incorrect surgeries) due to misdiagnosis.
- **Hospitalizations and Emergency Care:** Many patients experience acute crises (e.g., metabolic crises in certain enzyme disorders, severe seizures in epilepsy syndromes, acute organ failures) that lead to ER visits and ICU stays, which are very costly. For example, a child with a rare metabolic condition like MSUD (Maple Syrup Urine Disease) may have repeated hospital admissions for metabolic decompensations if not well-controlled.
- **Chronic Treatment Expenses:** If a rare disease has a treatment, it's often very costly (as we've seen with orphan drug prices). Enzyme replacement therapies can cost hundreds of thousands per year per patient. Organ transplantations (sometimes needed for rare diseases affecting liver, heart, lungs) have high upfront costs and lifelong maintenance with immunosuppressants. Even "standard" care like physical therapy, dietary supplements, and routine specialist follow-ups can accumulate significant costs over a lifetime.

- **Multi-disciplinary Care:** Rare disease patients often need a team – e.g., the average cost per year for a child with complex disabilities including medical equipment, multiple specialists, and therapy services can be very high. For instance, consider a child with a rare genetic syndrome causing developmental disability and complex organ issues – they might see neurologists, cardiologists, orthopedic surgeons, etc. each year, plus require special education and rehab services, many of which are funded by public health or school systems (blurring medical vs. non-medical costs).
- **End-of-Life Care:** Many rare diseases are life-limiting. End-of-life care (like hospice or intensive interventions in a hospital) also contributes to direct costs.

**Indirect Costs:** The indirect costs, as indicated in the U.S. study, can be nearly as large as the direct costs (<sup>[10]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)). Indirect costs essentially measure lost productivity – both of patients (when of working age) and their caregivers, as well as other societal opportunity costs. For rare pediatric diseases, the burden often falls on parents who may reduce work hours or leave jobs to care for their child. For adult patients with rare diseases, their illness might prevent them from maintaining employment. For example:

- If a young adult develops a rare autoimmune disease that is debilitating, they might drop out of the workforce, losing years of income and contributions to the economy.
- Parents of a child with a severe rare disease often become quasi full-time nurses, foregoing professional careers. A study by Rare Disease UK found that a significant percentage of caregivers reported cutting back on work or stopping work entirely due to their caregiving responsibilities [<https://www.rare-disease.org.uk/media/1588/ruheleder-et-al-rare-diseases-economic-burden-abstract.pdf>].
- Indirect costs also include premature mortality – the lost lifetime earnings of patients who die young. Rare diseases, many of which drastically shorten lifespan (e.g., progeria, Tay-Sachs, many childhood syndromes), represent lost economic potential. Though it's hard to quantify the value of a lost life in economic terms, economists do account for it in burden studies as an indicator of societal loss.
- Other non-medical costs (which can be considered indirect or a separate category) include things like home modifications (installing wheelchair ramps, special beds), travel expenses to see specialists (often rare disease patients have to travel across states or countries, incurring transport and lodging costs), and hiring of in-home care or nursing.

The U.S. study pegged indirect costs (productivity loss) at around **\$437 billion** (<sup>[10]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)), nearly equal to direct costs, and additional non-medical and uncovered health costs at another ~\$111 billion (<sup>[10]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)). In total, the **national economic burden approached \$1 trillion** just for the subset of rare diseases studied (<sup>[11]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)) (<sup>[18]</sup> [ojrd.biomedcentral.com](http://ojrd.biomedcentral.com)). This figure underscores that rare diseases, collectively, have a massive economic footprint – one that rivals common diseases and is a heavy load on society.

**Distribution of Costs:** It's also instructive to consider who bears these costs:

- Governments and healthcare systems bear a lot through funding of healthcare, especially in countries with national health services or Medicaid for disabled children.
- Private insurers bear some, in systems like the U.S., leading to higher premiums shared across society.
- Patients and families bear significant portions out-of-pocket. Many costs aren't fully covered – e.g., if insurance doesn't cover experimental treatments, or travel, or certain equipment. The financial burden on families can be catastrophic. Many families fundraise for medical expenses (the prevalence of GoFundMe campaigns for rare disease treatments attests to this).
- Productivity losses are borne by employers as well in terms of lost work output, and by public assistance programs if families need social support due to loss of income.

**Financial Hardship:** Surveys indicate rare disease families frequently face financial strain. A EURORDIS study across European countries found that a sizable percentage of rare disease patients/families had difficulty paying their bills or had to cut down on basic necessities due to the cost of medical care [<https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01778-5>]. In the U.S., many rare disease patients hit insurance lifetime caps or face high co-pays, historically leading some to personal bankruptcy (though ACA reforms improved some aspects like eliminating lifetime caps). There are instances of families having to sell homes or rely on community charity to afford treatments.

## Societal and Intangible Impacts

Beyond the dollars, rare diseases carry social implications:

- **Education and Development:** Many rare diseases affect children's cognitive and physical development, requiring special education services. Schools may need to accommodate children with rare conditions, which can mean training for staff, resource room assistance, or even in-school nursing. Some children can't attend regular school at all due to health, so society has to consider providing home or hospital-based education, or they might miss education entirely.
- **Labor Market and Talent Loss:** When an adult's career is cut short by a rare illness or a potential future contributor's life is lost young, society loses out on talents and contributions beyond just monetary. Think of rare diseases that strike in mid-life – these individuals might have been experts, workers, caregivers themselves, etc. Removing them from the social fabric has ripple effects (sometimes colleagues or family members also change their life paths to adjust).
- **Research and Innovation Externalities:** On the positive side, investments in rare disease often drive innovation that helps society broadly (as previously noted, many scientific breakthroughs from rare disease biology have informed common disease treatments). So there's a societal benefit to focusing on rare diseases in terms of knowledge gained. This is an argument some policymakers use to justify funding rare disease research – not just compassion, but the notion that it can yield general health insights (e.g., studying progeria gives clues about normal aging).
- **Community and Social Services:** Rare disease patients often rely on community social services – for example, disability benefits, respite care programs, or support from non-profits. The strain on these services grows as more rare disease patients are identified and seek support. Societies need to ensure these safety nets are equipped to handle rare conditions, which might require specialized training (like social workers who understand a particular rare disease's needs).
- **Equity and Inclusion:** There's a social justice aspect: historically, rare disease patients felt marginalized in healthcare priority setting. Recognizing rare diseases in global health agendas is partly about health equity – ensuring that even small patient groups have the right to care and life-saving treatment. This ties into larger values of an inclusive society: Do we value each life equally, even if saving that life costs more because the disease is rare? Ethicists debate how to balance cost-effectiveness with principles of equity. Many societies lean towards giving special consideration to the worst-off (e.g., those with severe rare diseases) which is an ethical argument for prioritizing some level of orphan drug funding despite high costs.
- **Quality of Life and Mental Health:** Rare diseases can severely impact the psychological well-being of patients and their families. Chronic stress, anticipatory grief (knowing a loved one has a shortened lifespan), and feelings of isolation can lead to mental health issues like depression, anxiety, and PTSD. This psychological toll is hard to measure in economic terms but is very real societally. It can manifest in increased use of mental health services or, if unaddressed, contribute to family breakdown or social withdrawal.
- **Stigma and Social Life:** Some rare diseases come with disfigurements or behavioral differences that can lead to stigma or social exclusion. For instance, a person with a rare skin disorder might face public

misunderstanding or bullying. Or rare metabolic disorders that cause intellectual disability may isolate families. Societal awareness and acceptance are improving, partly through advocacy and exposure (like Rare Disease Day campaigns), but stigma is still an issue. Reducing stigma and ensuring these individuals can participate in society (education, jobs, community activities) to their fullest ability is an important social goal.

**Caregiver Burden:** We touched on it earlier, but to emphasize: caregivers (often family members) of rare disease patients experience large burdens. They often have to become semi-professionals in nursing and case management without formal training. This can lead to burnout, affecting their health. Society may need to provide support systems for caregivers – respite care, counseling, support groups – to maintain their well-being. The intangible value of what caregivers provide (often uncompensated) is huge; one could try to assign an economic value (e.g., if the state had to pay professional caregivers for all that work, it'd be enormous).

**Demographic Considerations:** Rare diseases collectively affect all ages, but many are pediatric onset. This means a lot of the burden is in the pediatric healthcare system and in younger families. Countries with aging populations might not see as heavy a direct rare disease burden in the elderly, but they see it in the pediatric and young adult demographics. For instance, in Europe an estimated 50% of rare disease patients are children <sup>[62]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)), which impacts pediatric hospital resources heavily (some studies indicate rare disorders occupy a significant percentage of pediatric ICU beds at any given time). Ensuring pediatric health systems are well-resourced is a societal priority influenced by rare disease prevalence.

**Opportunity Cost of Not Treating:** There's also an argument that effective treatments for rare diseases, while expensive, may pay off economically if they restore individuals to health such that they can lead productive lives. For example, someone with a rare blood disorder cured by a gene therapy might avoid decades of medical costs and return to work, contributing to the economy. Even at high upfront cost, the long-term savings and productivity gain might outweigh it. Sickle cell disease (often considered a "rare" disease in some contexts) is an illustrative example: it's been calculated that curing a person with sickle cell with a gene therapy costing \$2M could actually be cost-saving over their lifetime because of averted healthcare costs and regained productivity [[https://ashpublications.org/blood/article/134/Supplement\\_1/4634/424266/Gene-Therapy-in-Sickle-Cell-Disease-A-Cost](https://ashpublications.org/blood/article/134/Supplement_1/4634/424266/Gene-Therapy-in-Sickle-Cell-Disease-A-Cost)].

For many ultra-rare diseases, such analysis is harder, but the principle stands: not treating means continued high medical spend and lost human potential. Treating means heavy upfront or ongoing costs, but possibly less downstream burden and a person who can engage more fully in society.

**Global Societal Effects:** In low- and middle-income countries (LMICs), rare disease patients often have it even harder in terms of economic and social support. Many LMICs don't have structured rare disease policies or insurance covering expensive interventions. This can lead to tragic situations where treatable rare diseases go untreated simply due to geography and income. There's a brain drain aspect too – families with means in some countries will relocate to countries where their child can get treated, leading to migration and concentration of demand for services in wealthier countries. Also, untreated rare diseases contribute to childhood mortality in LMICs – for example, in countries without newborn screening and good metabolic care, some portion of infant deaths are likely undiagnosed metabolic or genetic conditions. From a global health view beyond the humanitarian aspect, losing children to rare diseases and having others severely disabled who might have been treated if born elsewhere raises ethical and development issues.

All these factors highlight that addressing rare diseases is not just a matter of medical care but resonates with societal values and priorities. A society that commits to rare disease support tends to be one that values compassion, equity, and innovation. The adoption of rare disease strategies and the increase of funding is partly a reflection of societies recognizing these illnesses as an important component of public health that can no longer be ignored.

In conclusion, the economic and societal impacts of rare diseases provide a compelling argument for investment in rare disease research, healthcare infrastructure, and supportive policies. Such investments can reduce the long-term economic burden by improving efficiency of care and enabling patients (and caregivers) to participate more in society. More importantly, they alleviate tremendous human suffering and uphold the principle that every life has value, aligning economic decisions with ethical imperatives.

## Future Directions and Emerging Trends

Looking ahead, the landscape of rare diseases in the coming decade and beyond is poised for significant evolution. Advances in science and technology, coupled with growing policy momentum, are converging to address many of the long-standing challenges in rare diseases. Here we outline some key future directions and emerging trends that will likely shape the rare disease field around and after 2025.

### Genomic Medicine and Early Detection

One clear trend is the increasingly central role of genomics in rare disease diagnosis and prevention. The cost of DNA sequencing continues to fall, opening the door to more widespread use:

- **Expanded Newborn Screening (NBS):** Traditional NBS uses biochemical tests to screen for ~30-50 conditions. There is active research into using **whole genome sequencing (WGS)** or **whole exome sequencing (WES)** as a supplement to NBS. Pilot programs (like the BabySeq project in the U.S. and a planned large-scale study in the UK aiming to sequence 200,000 babies [<https://www.genomicsengland.co.uk/news/uk-newborn-genomes-programme-announcement>]) are evaluating the feasibility and ethics of sequencing newborns to detect a wider range of genetic conditions beyond the standard panel. By 2030, it's plausible that some jurisdictions will offer newborn genomic sequencing, either universally or for newborns who fail standard screens, enabling earlier diagnosis of many rare conditions that currently evade early detection. Key challenges – such as managing variants of uncertain significance, ensuring privacy, and deciding which results to report – are being addressed by policy working groups.
- **Carrier Screening and Preconception Genomics:** Another preventative approach is wider carrier screening for prospective parents. Currently, carrier screening is routine for certain conditions in specific populations (like Tay-Sachs in Ashkenazi Jews, or cystic fibrosis in Caucasians). In the future, more couples might opt for expanded carrier panels or even full exome sequencing to understand their risk of having a child with a rare recessive disease. This can inform family planning decisions or lead to using IVF with preimplantation genetic testing to avoid passing on known serious conditions.
- **Cascade Testing:** Once a rare genetic disease is identified in a family, testing of relatives (cascade screening) will likely become more streamlined. This helps identify others who might be at risk or be carriers, and allows earlier intervention. For example, in some inherited cancer syndromes (like familial medullary thyroid carcinoma), finding a mutation in a child prompts testing siblings who, if positive, can have prophylactic surgeries that are curative.
- **Long-read and New Sequencing Technologies:** To catch the remaining ~5-10% of undiagnosed cases after standard tests, new genomic technologies are emerging. **Long-read sequencing** (from companies like PacBio and Oxford Nanopore) can resolve structural variants and repeat expansions that short-read sequencing misses – this could identify mutations in rare diseases that were unsolvable before. **Whole genome sequencing** also captures non-coding mutations that WES might miss, which could unveil novel disease mechanisms (as with Mila's case – a retrotransposon insertion best seen on whole genome sequencing). By 2025+, expect more routine use of WGS, long-read, and transcriptome sequencing in

difficult undiagnosed disease cases, raising the diagnostic yield closer to 70–80% in genetic rare diseases versus ~50% today [<https://www.nature.com/articles/s41436-018-0006-8>].

- **AI in Diagnosis:** Artificial intelligence will likely play an increasingly prominent role. Machine learning algorithms can scan medical records and flag patterns suggestive of rare diseases (some EHR systems are developing rare disease “triggers” – e.g., if a patient has combinations of unusual lab results or repeated hospitalizations, an alert suggests considering a rare metabolic disorder). Image analysis AI tools might help radiologists spot rare disorder-specific findings on MRIs or X-rays that a general radiologist might overlook. And tools like Face2Gene will get more refined, potentially integrating voice analysis (some rare diseases have distinctive voice or speech patterns) or gait analysis, etc.
- **Global Data Sharing:** In the future, diagnosing an ultra-rare disease will increasingly involve tapping into global databases. The *Global Alliance for Genomics and Health* promotes sharing genomic and clinical data; platforms like the Matchmaker Exchange already connect clinicians to find another patient in the world with the same mysterious variant. By 2030, we might have a more seamless way where a clinician can input a patient’s genomic data into a secure network and find matches or similar cases worldwide instantly. This will help identify new syndromes faster and get patients a diagnosis by linking their case to known ones elsewhere.
- **Point-of-Care Genetics:** Another emerging trend is making genetic testing easier and faster at point-of-care. For acute neonatal or pediatric ICU cases, rapid sequencing (48-hour genome results) is becoming feasible and can diagnose critically ill infants in real time [<https://pubmed.ncbi.nlm.nih.gov/29100083/>]. The technology could trickle into broader hospital use. One can envision in a decade that if a child presents with unexplained seizures and developmental delay, a genomic test might be done within days in the hospital, rather than months after referrals.

## Therapeutic Advancements

On the treatment front, numerous exciting developments are on the horizon:

- **Gene Therapy 2.0:** We are already in first-generation gene therapies for a handful of diseases. Future improvements will involve:
- **Better Vectors:** New AAV capsids being engineered for more efficient delivery to specific organs (e.g., improved crossing of the blood-brain barrier for neurological diseases, or better uptake in muscle for muscular dystrophies). Also, non-viral delivery (like lipid nanoparticles for gene editing payloads) could open gene therapy to more conditions without immunogenicity issues of viruses.
- **Gene Editing:** CRISPR-based treatments should reach clinical practice for some conditions. The first ex vivo CRISPR therapy (for beta-thalassemia and sickle cell) might be approved around 2025–2026, and in vivo CRISPR (like Intellia’s ATTR amyloidosis treatment) is advancing. Next-generation gene editors (base editors and prime editors) offer the ability to correct point mutations more precisely without full DNA breaks, which might be safer. By 2030, we may see base editing clinically used for diseases like progeria or metabolic diseases by directly fixing the mutation in patient cells. One big goal is in vivo gene editing for dominant diseases – e.g., turn off a toxic gene (like the mutant huntingtin gene in Huntington’s disease) or fix a mutation in a large organ system.
- **Gene Therapy for Common Pathways:** Some technologies might be applied to multiple diseases, reducing development time. For instance, a “platform” that can insert a corrective gene into liver cells can be reused for many enzyme deficiency disorders by swapping the gene of interest, with much of the development work already done.
- **Safety and Regulatory Learning:** As more patients get gene therapies, knowledge about long-term safety (risk of cancer, issues with viral integration, etc.) will accumulate. Regulators might also get more

comfortable approving gene therapies on limited data if early results show dramatic benefit, given the often clear mechanism and one-time nature. There might also be innovation in manufacturing to reduce costs, e.g., better bioreactors for AAV production, which could help lower prices.

- **mRNA Therapies Post-COVID:** The success of mRNA vaccines accelerated interest in mRNA therapeutics. Several biotech companies are working on mRNA treatments for rare metabolic disorders, where mRNA can encode a protein missing in patients. For example, mRNA for **propionyl-CoA carboxylase** to treat propionic acidemia is in early trials (Moderna's program). mRNA could also be used to make enzymes for urea cycle disorders, or as a way to deliver gene editing tools (Cas9 mRNA + guide RNAs). The advantage is that mRNA isn't permanent (so safer for some contexts) and production is faster (you can design an mRNA for any protein relatively quickly). By the late 2020s, we might see mRNA treatments as a sort of "on-demand protein therapy" for conditions that currently need recombinant proteins or where gene therapy is too risky.
- **Antisense and RNAi Expansion:** The pipeline of antisense oligonucleotides and RNAi drugs for rare diseases will grow. Dozens are already in clinical trials for targets ranging from neuromuscular disorders (e.g., ASOs for various muscular dystrophies) to neurological conditions (ASOs for Huntington's, ALS, etc.), to renal diseases. The success of the first ones (Spinraza, eteplirsen, etc.) paved the way. By 2030, many rare genetic diseases that are due to toxic gain-of-function or dominant-negative mutations might be treatable by ASOs that silence the mutant gene or correct splicing. Delivery to new tissues is a focus – currently ASOs are good for central nervous system (intrathecal injection) and liver (systemic works well for liver-targeted GalNAc-conjugated siRNAs). Research is ongoing to target ASOs to muscle, heart, etc. Achieving broad distribution will expand what diseases can be tackled.
- **Targeted Small Molecules & Repurposing:** Not to be overlooked, small molecule drugs including **stop-codon readthrough agents, chaperones, modulators of signaling pathways** may address certain rare diseases. For example, in development are molecules that stabilize misfolded proteins in diseases like Marfan syndrome or that tune overactive pathways in developmental syndromes. Also, drug repurposing databases aided by AI might find existing drugs that can help rare conditions. E.g., sirolimus (rapamycin) is being tried in many rare diseases where the mTOR pathway is implicated (like certain syndromes with overgrowth). As computational biology improves, *in silico* screening might match rare disease molecular signatures to approved drugs (this is already being explored, e.g., using LINCS database which has gene expression profiles of cells treated with many compounds, to find if any drug's effect counteracts the gene expression signature of a particular rare disease).
- **Personalized Medicine at Scale:** Building on the N-of-1 example, efforts like the n-Lorem Foundation aim to create a sustainable pipeline for personalized ASOs for ultra-rare individuals. If technology and regulatory pathways mature, hundreds or thousands of patients with ultra-rare mutations might get individualized therapies. This will require innovative funding models (likely philanthropic or government-supported due to no commercial incentive for one-patient drugs) and possibly manufacturing automation (ASOs can be synthesized relatively easily, so maybe a central facility could churn out multiple custom ASOs under one quality system). Regulators might allow umbrella trial protocols to treat multiple single-patient "trials" more efficiently.
- **Smart Clinical Trials and Real-World Evidence:** For ultra-rare diseases, traditional RCTs often aren't feasible. The future will see more creative trial designs: basket trials (one drug, multiple diseases if they share a pathway), n-of-1 cross-over trials, Bayesian adaptive trials where prior data inform ongoing analysis. Use of **real-world evidence** (RWE) may allow approval based on patient registry data or historical controls more often. Digital natural history data (like tracking patient mobility via wearables) could serve as outcome measures, reducing need for large control arms. Regulators are warming to RWE particularly for post-market confirmation of benefit in rare disease drugs approved on limited initial data.
- **Regenerative Medicine and Cell Therapy:** Some rare diseases, especially those causing organ damage, might benefit from regenerative approaches. For example, gene-edited cell therapies like CAR-T are being trialed for rare autoimmune diseases (recently, a handful of lupus patients achieved remission with CAR-T

therapy [<https://www.nature.com/articles/d41586-022-02954-2>]). Rare hematologic or immunological disorders could see cures via gene-edited hematopoietic stem cell transplants (ex vivo editing to correct a genetic immune deficiency and then transplant back – a path similar to gene therapy but using the patient’s own cells). Tissue engineering might one day address rare diseases requiring organ replacement: bioengineered organs or gene therapy to reduce transplant rejection (making xenotransplants possible, etc.). These remain longer-term, but progress is steady.

## Policy and Collaboration

- **Global Action Plan Implementation:** Following the WHO’s directive (<sup>[4]</sup> [www.rarediseasesinternational.org](http://www.rarediseasesinternational.org)), we can expect by late 2020s a formal global rare disease action plan. This might include setting targets like: each country to have a rare disease registry, X% of rare disease patients to be diagnosed within 1 year by 2030, Y number of new therapies developed, etc. It will also likely encourage international collaboration (for example, pooling research in a global rare disease research fund, or sharing best practices in care).
- **National Plans in More Countries:** More countries, including middle-income countries, will formulate rare disease strategies. Already places like India released a National Rare Disease Policy in 2021 focusing on tertiary care centers and crowdfunding for expensive drugs [<https://pib.gov.in/PressReleasePage.aspx?PRID=1707707>]. By 2030, ideally, most countries will have some policy acknowledging rare diseases, even if just to coordinate referrals or subsidize key treatments (like India’s plan to fund one-time curative therapies like gene therapy up to a certain cap).
- **Improved Access and Affordability:** Due to pressure from patient advocacy and ethical arguments, we might see novel models to pay for orphan drugs. For instance, cross-border healthcare agreements where countries jointly purchase expensive therapies to get volume discounts, or international funds (perhaps through organizations like UN or World Bank) to help low-income nations afford certain life-saving orphan drugs for diseases like Gaucher or SCID. If gene therapies for prevalent global conditions like sickle cell become approved, ensuring equitable access in Africa where SCD is not rare will be a huge test – possibly prompting subsidized programs or differential pricing (like how HIV drugs are provided at lower cost in Africa via global programs).
- **Orphan Drug Policy Reform:** In regions like the EU, lawmakers are reviewing orphan drug regulations for tweaks: potential changes include adjusting market exclusivity periods or obligations to market in all member states to maintain exclusivity. The aim is to fill the gaps where orphan drugs get approved but not launched in smaller markets, and to encourage focus on ultra-rare diseases that still lack treatments. Similarly, in the US, after some controversies of “gaming” the system, there could be refinements to ensure orphan incentives truly go to novel needed drugs and not modifications of existing ones for profit extension. Nevertheless, incentives will likely remain robust because they have clearly stimulated development.
- **Patient Voice Integration:** The future will likely see even stronger involvement of patient representatives in all aspects: research priority setting, clinical trial design, regulatory review (FDA already includes patient representatives in advisory committees sometimes, and “patient experience data” is considered). The concept of patient-centered outcome measures will be key – e.g., if a new drug doesn’t change a lab number but patients *feel* much better or function better in daily life, that will carry weight. Regulatory science is evolving to better capture such outcomes (using tools like digital health records, wearable sensors for continuous data, etc.).
- **Telehealth and Care Networks:** One positive shift from the COVID-19 era is normalization of telemedicine, which is a boon for rare disease care. Many rare disease patients live far from specialists; telehealth can allow them to consult experts without travel. This will likely persist and expand – maybe even global teleconsults where, for instance, a physician in Brazil can have a joint telehealth appointment with a patient and a specialist in the US to strategize care. The infrastructure and licensing issues will need smoothing, but clinically it makes sense especially for advice on complex cases.

- **Holistic Support Systems:** Recognizing the multi-dimensional needs, more holistic rare disease centers might develop. For example, *Rare Disease Centers of Excellence* that provide not only medical care but also genetic counseling, mental health support, social work to help with insurance and resource coordination, and connections to patient advocacy groups. Some leading children’s hospitals (e.g., Children’s Hospital of Philadelphia) have started such integrated clinics for undiagnosed or complex rare disease patients. This model could spread, improving quality of life and outcomes.
- **Education and Training:** Medical education in 2025+ will likely incorporate more on rare diseases and genetics. Already some med schools have programs where patients with rare conditions come talk to students (“Patients as Teachers”) to build awareness. There may be accredited training programs for “Genetic Medicine” or “Rare Disease Medicine” specialties developing, analogous in some way to how oncology or cardiology are specialties. For instance, the role of the “medical geneticist” could expand or differentiate – perhaps one track focusing on lab genetics, another on clinical rare disease management. More broadly, empowering general practitioners with tools and knowledge for rare disease suspicion and initial management will be crucial, since they are the front-line.
- **Community and Global Solidarity:** The rare disease community’s mantra “Alone we are rare, together we are strong” will continue to foster solidarity not just among patients but among nations. The establishment of international observances (Rare Disease Day) and alliances (like Rare Diseases International, Asia-Pacific Alliance, etc.) will strengthen. We might see joint international studies (sharing data to increase sample size for ultra-rare disease research, for example, through IRDiRC collaborations) and more cross-border policies (like European Reference Networks allowing patients in one country to access expertise from another virtually – that concept might extend beyond Europe in the future).
- **Ethical Considerations:** As we cure or treat more diseases, ethical questions will also arise. If genome editing can eliminate a disease, should we? Applications of CRISPR in embryos, for instance, might be considered for eradicating severe genetic diseases (with all the attendant ethical debates about germline editing). Also, how do we prioritize which disease to tackle next – should we focus resources on a slightly less rare condition that affects thousands, or an ultra-rare one affecting ten people with no cure? Transparent and inclusive decision-making frameworks will be needed, likely involving ethicists, patient representatives, and public commentary.

In envisioning the future, it’s easy to be optimistic given the rapid advances of late. However, numerous challenges will persist:

- Many diseases lack understanding of basic biology – research must continue to reveal targets for therapy.
- The cost of new therapies, especially gene therapies, might strain economies, requiring innovation in financing (like health bonds or outcomes-based models).
- Ensuring the benefits of research reach all populations, not just those in wealthy countries or those with certain ancestries (genomic research has been Eurocentric; more effort is needed to include diverse populations to ensure tests and treatments are effective for all genetic backgrounds).
- Preventing a “treatment divide” where some rare diseases get multiple therapies (like some genetic cancers have many targeted drugs now) while others remain neglected because they are less known or harder to solve – policy incentives might need to be tweaked to cover the truly hard-to-treat ultrarare conditions.

Despite these challenges, the momentum in rare disease awareness, science, and collaboration suggests that by 2030 and beyond, the rare disease landscape will be markedly improved:

- More patients will get answers (higher diagnostic rates, fewer long odysseys).
- A greater fraction of rare diseases will have at least one therapy, possibly bringing that 5% figure in 2025 closer to 10-20% by 2035 (with emphasis on the more common of the rare diseases initially, but also some ultra-rares via bespoke therapies).

- Patients will live longer and with better quality, transforming certain diagnoses from fatal in childhood to chronic conditions manageable into adulthood (following the footsteps of CF and SMA).
- Societal integration will improve – less stigma, better support – with rare disease considerations woven into general healthcare planning and social services.

In summary, the future of rare diseases is one of accelerating progress and convergence of fields – genetics, digital health, advanced therapeutics, policy, and patient advocacy – all driven by the shared goal that no disease should be left without hope simply because it is rare. The ultimate vision can be encapsulated in IRDIRC's audacious goal: that **all people living with a rare disease will receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention** (<sup>[63]</sup> [irdirc.org](https://irdirc.org)). Achieving that will take time, investment, and global commitment, but as the developments of the past few years have shown, it is an increasingly tangible aspiration rather than a distant dream.

## Conclusion

Rare diseases, once largely overlooked, have in recent years moved to the forefront of scientific innovation and global health discussions. The landscape of rare diseases in 2025 is markedly different from that of a few decades ago: there is greater awareness, stronger advocacy, burgeoning research, and a pipeline of new diagnostics and therapies that are bringing hope to patients and families who previously had none. This comprehensive examination of the rare disease landscape has highlighted the extraordinary progress made – as well as the significant challenges that remain.

**Reflecting on Progress:** We have seen that through targeted incentives like the Orphan Drug Act and global collaborations, over one thousand orphan therapies have been approved, directly benefiting patients with conditions like cystic fibrosis, spinal muscular atrophy, various enzyme deficiencies, and more. Pioneering technologies such as gene therapy, antisense oligonucleotides, and small-molecule modulators have transformed once-lethal diseases into manageable conditions in some cases. The diagnostic odyssey, while still too long, has been shortened for many by advances in genomic sequencing and the concerted efforts of initiatives like Undiagnosed Disease Programs and international data-sharing. Perhaps most inspiring are the individual stories – the children with SMA who are now thriving due to early treatment, the teens with progeria who gained precious extra years from a repurposed drug, and the singular case of Mila where personalized medicine offered a bespoke treatment. These are testaments to human ingenuity, perseverance, and the power of aligning science with compassionate purpose.

**Current State – Challenges Persist:** Despite these successes, it is clear that the journey is far from over. Approximately **95% of rare diseases still have no FDA-approved treatment** ([projects.research-and-innovation.ec.europa.eu](https://projects.research-and-innovation.ec.europa.eu)). Millions of patients around the world are still waiting for their first effective therapy. Delays in diagnosis average several years (<sup>[19]</sup> [www.eurordis.org](https://www.eurordis.org)), with some patients remaining undiagnosed or misdiagnosed entirely. The **economic burden** of rare diseases is vast – nearly a trillion dollars a year in the US when considering medical and non-medical costs (<sup>[11]</sup> [ojrd.biomedcentral.com](https://www.nature.com/articles/nrn3811)) – reflecting inefficiencies in care and lack of preventive treatment, as well as the high cost of emerging therapies. Patients and families endure significant psychosocial stress and financial hardship. Even when drugs exist, **access inequity** is a major issue: high prices and divergent health system resources create an environment where some lifesaving treatments are out of reach for patients in low-income settings or without adequate insurance. These challenges underscore that scientific breakthroughs alone are not enough; they must be coupled with supportive policies and systems to ensure delivery to those in need.

**Multi-Stakeholder Collaboration – A Key Theme:** Throughout this report, one recurring theme is that progress in rare diseases is maximized when all stakeholders work in concert. Patients and advocacy groups bring urgency, focus, and often act as the glue connecting researchers, clinicians, and funders – the success of

therapies for CF, SMA, and others bear the imprint of patient advocacy at every step. Healthcare providers on the front lines are crucial for early suspicion and compassionate long-term care, and they benefit from and contribute to networks of expertise such as centers of excellence and international collaborations. Researchers drive the engine of discovery, and in rare diseases they have shown how thinking outside the box (as with Mila's customized drug) can accelerate solutions. The pharmaceutical industry, incentivized appropriately, has demonstrated that it can develop and deliver orphan drugs at a remarkable pace – but also holds the responsibility to price and market these ethically and sustainably. Policymakers and regulators, for their part, create the conditions for success through legislation, funding of research and care, and ensuring that frameworks adapt to the unique needs of rare conditions (for example, approving drugs on surrogate endpoints or fostering data-sharing initiatives).

**Looking to the Future:** The horizon for rare diseases is hopeful. We can reasonably anticipate that by the end of this decade:

- **Diagnostic rates will improve**, possibly aided by genome sequencing becoming a routine part of medical evaluation, leading to more patients receiving answers in infancy or childhood rather than after years of uncertainty.
- **Therapeutic options will expand** – the number of treatable rare diseases will grow with the maturation of gene therapies, RNA therapies, and other modalities. Conditions like sickle cell disease and various inherited retinal diseases might see gene editing cures; numerous neurologic and metabolic disorders currently untreatable could have their first dedicated medications.
- **Patient outcomes will improve**, with longer lifespans and better quality of life. Diseases that once implied a short, painful life may evolve into chronic conditions where patients can go to school, work, and have families of their own. We've already seen this shift in cystic fibrosis and are beginning to see it in others.
- **Global initiatives** will likely reduce disparities – with the WHO's rare disease action plan galvanizing efforts to include rare diseases in universal health coverage goals, ideally more patients in low-resource settings will benefit from diagnostics and therapies.
- **Integrated care models** will become more common, addressing not just the medical but the educational, social, and psychological needs of rare disease patients and their caregivers. This holistic approach can mitigate some indirect costs and burdens.

However, these positive trajectories are not guaranteed; they require sustained commitment. The progress in rare diseases to date has been hard-won and often fragile – reliant on continued funding (public and private), supportive policy environments, and the goodwill of collaborative networks. Economic pressures (such as debates on drug pricing or health budget constraints) could threaten the viability of orphan drug development or access. Ethical dilemmas (like gene editing) will need careful navigation to maintain public trust. The rare disease community – a coalition of patients, families, clinicians, scientists, industry leaders, and policymakers – must continue to champion the cause and innovate around roadblocks.

**Closing Reflections:** The late Dr. Jonas Salk, when asked about who owns the patent on the polio vaccine, famously responded, "Could you patent the sun?" His sentiment was that some advancements are so critical to humanity that they belong to everyone. In a similar spirit, one might argue that solutions for rare diseases, albeit benefiting smaller populations, represent a collective triumph of humanity over one of its most poignant challenges – the randomness of genetic fate. Every child cured of a "rare" disease is a child restored to their family, community, and the world of possibility; the ripple effect of that is immeasurable.

Rare diseases teach us that **every life matters**, no matter how uncommon the condition. They push the frontiers of science and ethics, prompting us to ask not just "Can we solve this?" but "Will we dedicate ourselves to solving this?" The evidence so far shows that when we do decide to act – as with the Orphan Drug Act, as with the international collaborations and the passionate advocacy – we can achieve the extraordinary.

In conclusion, the 2025 landscape of rare diseases is one of both unprecedented opportunity and ongoing responsibility. We stand at a point where the convergence of knowledge, technology, and empathy can drastically alter what it means to live with a rare disease. The path forward will require continued **depth of research, breadth of collaboration**, and unwavering **commitment to equity**. If these are maintained, the next decades will see many more “rare” victories – each one a testament to the idea that in alleviating the burdens of the rarest among us, we elevate the health and humanity of society as a whole.

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