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REVIEW

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Rare diseases: a comprehensive literature review and future directions

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Abstract

Rare diseases (RDs) affect a small percentage of the population but collectively impact millions worldwide. Their diagnosis and treatment remain challenging due to clinical heterogeneity, limited research, and high costs. Advances in genomics, artificial intelligence, and orphan drug development have improved diagnostic precision and therapeutic options, yet access disparities persist. Patients face not only medical challenges but also significant psychosocial burdens. Addressing these issues requires interdisciplinary collaboration, increased research funding, and policy reforms to accelerate drug development and improve healthcare accessibility. Innovative solutions like telemedicine and data-sharing networks can bridge existing gaps. This article explores the current landscape of rare disease research, highlighting challenges and potential strategies to enhance diagnostics, treatment, and patient care. This review emphasizes the need for targeted interventions by highlighting recent advances such as CRISPR-Cas9 and AI-assisted diagnostics, which have shown transformative potential in improving early detection and treatment of rare diseases. This review further addresses the importance of real-world evidence (RWE), mental health integration, patient advocacy, and regulatory frameworks in shaping equitable and effective rare disease strategies. A conceptual framework is proposed to unify key challenges, stakeholders, solutions, and outcomes, offering a holistic path forward.

Background

Rare diseases (RDs) are a heterogeneous group of conditions, each affecting a small percentage of the population, but collectively impacting a significant number of individuals worldwide [1]. These disorders are often chronic, debilitating, and life-threatening, posing substantial challenges for those affected, their families, and healthcare systems [2]. Defining a rare disease varies across regions, and although criteria differ, it is widely reported in the literature that between 6,000 and 8,000 rare diseases have been identified globally [3–5]. Recent estimates, based on advances in genetic diagnostics, indicate this number may surpass 10,000, with a global prevalence affecting approximately 263 to 446 million individuals, or 3.5% to 5.9% of the world's population [3–6]. The characteristics of rare diseases include a wide range of symptoms and clinical manifestations, making diagnosis complex and often delayed [7]. Many RDs are genetic in origin and are often chronic and incurable [8]. The lack of awareness among healthcare providers, coupled with limited diagnostic and therapeutic resources, further exacerbates the difficulties in managing these conditions [7].

The impact of rare diseases extends beyond the individual, affecting families emotionally, financially, and socially [9]. Caregivers often face immense burdens, including managing complex medical needs, navigating healthcare systems, and providing psychological support [10]. The healthcare system also experiences significant strain due to the high costs associated with diagnosis, treatment, and long-term care for individuals with RDs [11]. The distribution and prevalence of specific RDs can vary significantly across different geographical regions and populations [12]. For example, sickle cell disease (SCD) is considered rare in the EU but is relatively

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common in some African countries [13]. Similarly, amyotrophic lateral sclerosis (ALS) is an emerging focus of RD research in Africa, highlighting opportunities for further study [14]. In Nigeria, sickle cell crisis management highlights the urgent need for novel therapeutic solutions [15]. Given the significant challenges and unmet needs in the field of rare diseases, there is an urgent need for increased research, improved diagnostic tools, and the development of effective treatments [16]. To address these gaps, this review was conducted using a structured literature search across databases such as PubMed, Scopus, and Web of Science, covering publications from 2010 to 2024. Keywords included "rare diseases," "orphan drugs," "genomic diagnostics," "CRISPR," "gene therapy," "patient advocacy," "healthcare equity," and "AI in rare disease diagnosis." Articles were selected based on relevance, quality, and global representation, and the findings were organized thematically to offer a comprehensive overview of rare disease challenges and solutions.

Addressing these issues requires collaborative efforts from researchers, healthcare professionals, policymakers, and patient advocacy groups [17].

Existing research on rare diseases encompasses a wide range of topics, including epidemiology, genetics, pathophysiology, diagnosis, treatment, and psychosocial impact. Key findings from these studies highlight the complexity and heterogeneity of RDs, as well as the challenges in managing these conditions [1]. Major advancements in diagnosis and treatment have been made in recent years, driven by technological innovations and increased research efforts [2]. However, significant research gaps and limitations remain, hindering progress in improving outcomes for individuals with rare diseases. One major area of advancement is the use of genomic technologies for identifying the genetic causes of RDs [18]. Whole-exome sequencing and whole-genome sequencing have enabled the discovery of novel disease-causing genes and have improved diagnostic accuracy for many RDs [19]. These technologies have also facilitated the development of targeted therapies, such as gene therapies and personalized medicine approaches [20].

Another area of progress is the development of disease registries and databases for collecting and sharing data on rare diseases [17]. These registries serve as valuable resources for epidemiological studies, clinical research, and drug development [17]. By pooling data from multiple sources, researchers can overcome the challenges associated with small patient populations and gain a better understanding of the natural history and phenotypic diversity of RDs [17]. Despite these advancements, several research gaps and limitations remain. Many RDs still lack effective treatments, and the underlying mechanisms of many RDs are not fully understood [8]. Clinical trials for rare diseases are often difficult to conduct due to small patient populations and the heterogeneity of disease manifestations [21]. Additionally, there is a need for more research on the psychosocial impact of RDs and the development of interventions to support patients and caregivers [19].

Structured insights from recent studies and reports emphasize the importance of collaborative research, patient advocacy, and policy changes to address the challenges in rare disease management [22]. Academia-industry partnerships can accelerate drug development and improve access to innovative therapies [2]. Patient advocacy groups play a crucial role in raising awareness, promoting research, and supporting patients and families [9]. Policy changes, such as increased funding for rare disease research and streamlined regulatory pathways for ODs, can create a more favorable environment for developing and delivering treatments for RDs [23].

While previous literature has addressed many of the diagnostic, treatment, and policy challenges in rare disease management, gaps remain in integrating emerging technologies, addressing global disparities, and providing holistic patient support. Many existing reviews focus narrowly on high-income regions or biomedical aspects, often overlooking mental health, real-world evidence, and the role of patient advocacy in underserved populations. This review contributes a broader perspective by synthesizing developments in AI-assisted diagnostics, CRISPR-based therapies, global equity concerns, and psychosocial interventions. It highlights interdisciplinary and scalable strategies to bridge persistent gaps in RD research, care, and policy.

Challenges in rare disease research and treatment

Diagnostic challenges

Diagnosing rare diseases is often delayed due to limited awareness among healthcare professionals and the rarity of symptoms, which are frequently misattributed to more common conditions [7]. This lack of awareness can lead to a prolonged diagnostic odyssey, characterized by multiple specialist visits and invasive testing, often spanning several years [16]. The heterogeneity of rare diseases, with their diverse and overlapping symptoms, further complicates the diagnostic process [2]. Clinical manifestations can vary widely, even among individuals with the same genetic mutation, making it difficult to recognize and differentiate specific RDs from more common conditions [2]. This clinical heterogeneity necessitates specialized diagnostic tests and genetic screening to confirm suspected diagnoses [1]. Emerging next-generation DNA sequencing technologies have enhanced the ability to understand the pathophysiological mechanisms underlying many rare diseases [1]. However, the application

of these advanced technologies is often limited in developing countries due to resource constraints and lack of infrastructure [1]. Moreover, the interpretation of genetic data can be challenging, requiring expertise in bioinformatics and clinical genetics to identify causative mutations and distinguish them from benign variants [18]. For example, the use of whole-exome sequencing has greatly improved diagnosis in conditions like cystic fibrosis and Duchenne muscular dystrophy, enabling early intervention and personalized care. Genomic technologies, particularly next-generation sequencing (NGS) and whole-exome sequencing (WES), have significantly advanced the diagnosis and understanding of rare diseases. These tools have enabled faster and more precise identification of genetic mutations, especially in cases where clinical symptoms are ambiguous or overlap with more common conditions. Their application has been particularly impactful in diagnosing rare metabolic and neurodevelopmental disorders, which often present with nonspecific clinical features that make traditional diagnosis challenging [24–26]. Early and accurate genetic identification not only facilitates targeted treatment but also provides essential information for genetic counseling and long-term management [25, 26]. In pediatric neurology, NGS and WES have increased the detection rate of disease-causing genes, allowing for improved prognostic clarity and more personalized therapeutic strategies [24, 25]. Reanalysis of genomic data has also led to new diagnoses in previously unresolved cases, as ongoing discoveries and advances in bioinformatics continue to expand our understanding of gene-disease relationships [25]. Understanding the genetic basis of disease supports the use of next-generation therapeutics, including gene editing technologies, antisense oligonucleotides, and RNA-based treatments, many of which are now being explored as potential curative options for certain rare disorders [27]. Genetic diagnosis additionally strengthens family support mechanisms through more informed care planning, enhanced surveillance, and access to clinical trials and emerging therapies [24–27].

Limited treatment options

A significant challenge in rare disease management is the lack of targeted therapies for most RDs [8]. Due to the small patient populations, pharmaceutical companies often have limited commercial interest in developing drugs for rare diseases, leading to a scarcity of treatment options [8]. This lack of therapeutic options leaves many patients with RDs relying on symptomatic management and supportive care, which may not adequately address the underlying disease mechanisms [19]. For instance, in Nigeria, sickle cell crisis management relies heavily on supportive care, underscoring the need for innovative therapies [15]. An orphan drug (OD) is a medication specifically developed to diagnose, prevent, or treat rare diseases [28]. These conditions affect a small percentage of the population and are often life-threatening or chronically debilitating. Due to the limited number of affected individuals, pharmaceutical companies typically have little financial incentive to develop treatments under standard market conditions [28, 29].The development of orphan drugs (ODs) has been incentivized through legislation in the United States (1983) and the European Union (2000), aiming to encourage pharmaceutical companies to invest in rare disease treatments [13]. However, even when ODs are available, their high cost often poses a significant barrier to accessibility [13]. For instance, treatments for paroxysmal nocturnal hemoglobinuria (PNH) can cost hundreds of thousands of dollars per year, making them unaffordable for many patients, particularly in low-income countries [13]. Gene and cell therapies offer promising avenues for treating certain rare genetic diseases by targeting the underlying genetic defects [20]. Several gene therapies have been approved for rare diseases affecting the brain and spinal cord, including spinal muscular atrophy and metachromatic leukodystrophy [20]. However, these therapies are often complex, expensive, and not yet widely available, limiting their impact on the broader rare disease population [20].

The financial burden associated with rare disease treatments further complicates access, particularly for patients in low- and middle-income regions. Orphan drugs, while increasingly available, often come with prohibitive costs. In the United States, the median annual treatment cost for orphan drugs is approximately $218,872, while in France, it averages around €96,518 (equivalent to $100,000–$120,000) [30, 31]. Across Europe, these costs vary substantially, ranging from as low as £726 to as high as £378,000 annually [32]. Gene therapies, though promising in terms of disease-modifying potential, also carry significant financial implications. At the time of market entry, gene therapy prices in the U.S. and Europe have been reported between $200,064 and $2,125,000 [33], with other studies noting costs ranging from $447,600 to $1,020,000 in the U.S., and from $370,000 to $962,890 in Europe [34]. As of January 2022, the U.S. FDA had approved eight gene therapies and the European Medicines Agency (EMA) ten, with nearly all of them granted orphan designation [33]. A global survey in 2018 found 52 marketed cell and gene therapy products, of which 13 were gene therapies, and 66.7% of these held orphan designation [34]. The FDA's approval of orphan drugs has shown a rising trend between 2017 and 2021, indicating expanding interest and investment in this domain [30]. Despite this growth, affordability remains a major barrier. Gene therapies for rare genetic disorders can cost over $1

million per patient, and issues such as limited long-term outcome data and large up-front payments have raised concerns over equitable access [33, 34]. In countries like China, the average cost of a treatment course involving one of 23 orphan drugs is approximately $4,843.50, representing a cost that far exceeds average income levels and placing such therapies out of reach for most citizens [35]. Moreover, in the European context, branded orphan drugs have been reported to be 1.4 to 82,000 times more expensive than their generic counterparts, severely constraining their affordability and availability [32].

Funding and research gaps

Disparities in research funding between rare and common diseases pose a significant obstacle to advancing knowledge and developing new treatments for RDs [8]. Rare diseases often receive less attention and resources compared to more prevalent conditions, leading to slower progress in understanding their underlying mechanisms and identifying potential therapeutic targets [21]. This disparity is partly due to the perception that RDs affect only a small number of individuals, making them less attractive for large-scale research investments [21]. Securing grants for rare disease studies can be challenging, as funding agencies often prioritize research with broader public health implications [8]. Researchers working on rare diseases may face difficulties in demonstrating the potential impact of their work and competing with larger, more established research groups [8]. This limited funding can hinder the ability to conduct comprehensive studies, develop innovative diagnostic tools, and explore novel treatment strategies [8]. Low commercial interest in rare diseases further exacerbates the funding gap, as pharmaceutical companies may be reluctant to invest in drug development for small patient populations [22]. The high costs and risks associated with drug development, coupled with the limited potential for return on investment, can deter companies from pursuing rare disease therapies [22]. This lack of commercial interest necessitates alternative funding models, such as public–private partnerships and government incentives, to stimulate drug development for RDs [22].

Accessibility and equity issues

Unequal distribution of healthcare facilities and specialized expertise for rare diseases creates significant accessibility barriers for many patients [36]. Individuals living in rural or low-income communities often face challenges in accessing specialized diagnostic and treatment centers, which are typically located in urban areas [36]. This geographical disparity can lead to delayed diagnoses, inadequate treatment, and poorer outcomes for patients with RDs [36]. The COVID-19 pandemic further exposed these disparities in Africa, particularly for neurological disorder patients [37]. These inequities extend to neurological care in underserved populations, where access to specialized services remains limited [38]. Disparities in clinical trial participation further contribute to inequities in rare disease research and treatment [13]. Patients from underrepresented populations, including racial and ethnic minorities, often face barriers to participating in clinical trials, such as lack of awareness, language barriers, and mistrust of the healthcare system [13]. This lack of diversity in clinical trial populations can limit the generalizability of research findings and hinder the development of treatments that are effective for all patients [13]. Addressing these accessibility and equity issues requires targeted interventions to improve healthcare infrastructure in underserved communities and promote diversity in clinical trial participation [36]. Telemedicine and digital health solutions can help bridge geographical gaps and improve access to specialized care for patients with RDs [39]. Additionally, culturally sensitive outreach and education programs can increase awareness and promote trust among underrepresented populations, encouraging their participation in research and clinical trials [39].

Mental health impact

The psychological burden on patients and caregivers affected by rare diseases is substantial, often leading to increased rates of anxiety, depression, and other mental health disorders [10]. Patients with RDs may experience feelings of isolation, uncertainty, and hopelessness due to the challenges associated with diagnosis, treatment, and long-term management [10]. Similarly, during the COVID-19 pandemic, African patients with neurological disorders faced heightened isolation and reduced healthcare access, suggesting parallel challenges for RD populations [37]. Caregivers often face chronic stress, exhaustion, and emotional strain as they navigate the complex medical needs of their loved ones [9]. Lack of mental health support and resources further exacerbates the psychological impact of rare diseases [19]. Mental health services are often not integrated into the care pathways for RDs, leaving patients and caregivers without adequate access to psychological support [19]. This lack of support can lead to poorer mental health outcomes, reduced quality of life, and increased healthcare costs [19]. Support programs such as RareConnect and country-specific patient advocacy groups have been shown to improve psychological well-being by offering peer support, structured counseling, and reliable educational content for patients and caregivers. Addressing the mental health needs of patients and caregivers requires a multidisciplinary approach that integrates psychological support into the comprehensive care for rare diseases

Table 1 Summary of mental health interventions for rare disease populations

Citations	Intervention type	Target group	Reported benefits
Rice et al. [42], Kenny et al. [41]	Psychosocial/Supportive	Caregivers	Reduced stress, burden, and isolation
Depping et al. [43]	Peer-Delivered Self-Help	Patients	Improved disease acceptance, coping, social support, QoL
Bardon et al. [44]	Group Therapy	Patients	Reduced psychological impact, improved QoL, enhanced support
Lyon et al. [45], Boettcher et al. [46]	Family-Based Programs	Families/Caregivers	Improved mental health, family functioning, and well-being
Lyon et al. [45]	Advance Care Planning	Caregivers	Greater peace, meaning, reduced distress

[19]. Mental health professionals should be part of the healthcare team, providing counseling, therapy, and support groups to help patients and caregivers cope with the emotional challenges of living with a rare disease [19]. Additionally, raising awareness about the mental health impact of RDs and reducing stigma can encourage individuals to seek help and access available resources [39]. Patients and caregivers affected by rare diseases face significant mental health challenges, including elevated levels of anxiety, depression, stress, and isolation due to diagnostic delays, misunderstood symptoms, and limited treatment options [40]. Despite the severity of these psychological burdens, mental health services are often not well integrated into rare disease care pathways [41]. A summary of effective interventions and their outcomes is provided in the depicted in Table 1.

These multifaceted challenges such as spanning diagnosis, treatment, funding, access, and psychosocial impact, require coordinated efforts across stakeholders. A conceptual framework outlining these interconnected elements is presented in Fig. 1. This diagram illustrates the major challenges in rare disease management, the key stakeholders involved, proposed solutions, and expected outcomes. It highlights the need for a collaborative and multi-pronged approach to improve diagnosis, care, and equity for patients with rare diseases.

Future directions and recommendations

Advancements in diagnosis and treatment

Artificial intelligence (AI) and machine learning (ML) are poised to revolutionize the diagnosis and treatment of rare diseases [2]. AI and ML algorithms can analyze vast datasets of clinical, genetic, and imaging data to identify patterns and predict diagnoses with greater accuracy and speed [18]. These technologies can also be used to personalize treatment plans based on individual patient characteristics and predict treatment responses [2]. Precision medicine and genetic therapies hold immense promise for treating rare genetic diseases by targeting the underlying genetic defects [20]. Gene editing technologies, such as CRISPR-Cas9, offer the potential to correct disease-causing mutations and restore normal gene function [20]. However, CRISPR-Cas9 faces technical challenges such as off-target effects and limited precision, particularly in human embryos and germline cells [47]. Ethical concerns include heritable genetic alterations, informed consent, potential eugenics, and societal impacts [47, 48]. These issues underscore the need for rigorous oversight, transparent research, and inclusive public dialogue before clinical use [48][47, 49]. Personalized medicine approaches, such as drug repurposing and tailored therapies, can optimize treatment outcomes and minimize adverse effects [50]. Recent developments in N-of-1 therapies have opened the door to highly individualized treatments for ultra-rare diseases. These therapies are tailored to a single patient's unique genetic variant, as seen in examples like milasen, a custom antisense oligonucleotide therapy developed for a child with Batten disease [51, 52]. Pharmacogenomics is also increasingly applied in rare disease treatment by using genomic data to guide drug selection, dosage, and predict adverse reactions, enhancing both safety and efficacy [53, 54] (Barton et al., 2023; Williams et al., 2023). Furthermore, genetic mapping resources such as gnomAD and GenomeAsia provide large-scale variant frequency data that improve the accuracy of disease mutation identification and enable the development of more precise diagnostic tools [53, 54].

Strengthening collaborative research

Academia-industry partnerships are essential for accelerating the development of new diagnostic tools and therapies for rare diseases [2]. By combining the expertise and resources of academic researchers and pharmaceutical companies, these partnerships can facilitate the translation of basic research findings into clinical applications [2]. Collaborative research initiatives can also promote data sharing, improve study design, and enhance the efficiency of clinical trials [17]. Patient advocacy groups play a crucial role in driving rare disease research by raising awareness, mobilizing resources, and advocating for policy changes [9]. These groups can also facilitate patient participation in research studies, provide valuable insights into the patient experience, and ensure that research efforts are aligned with patient needs and priorities [9]. By empowering patients and families, advocacy

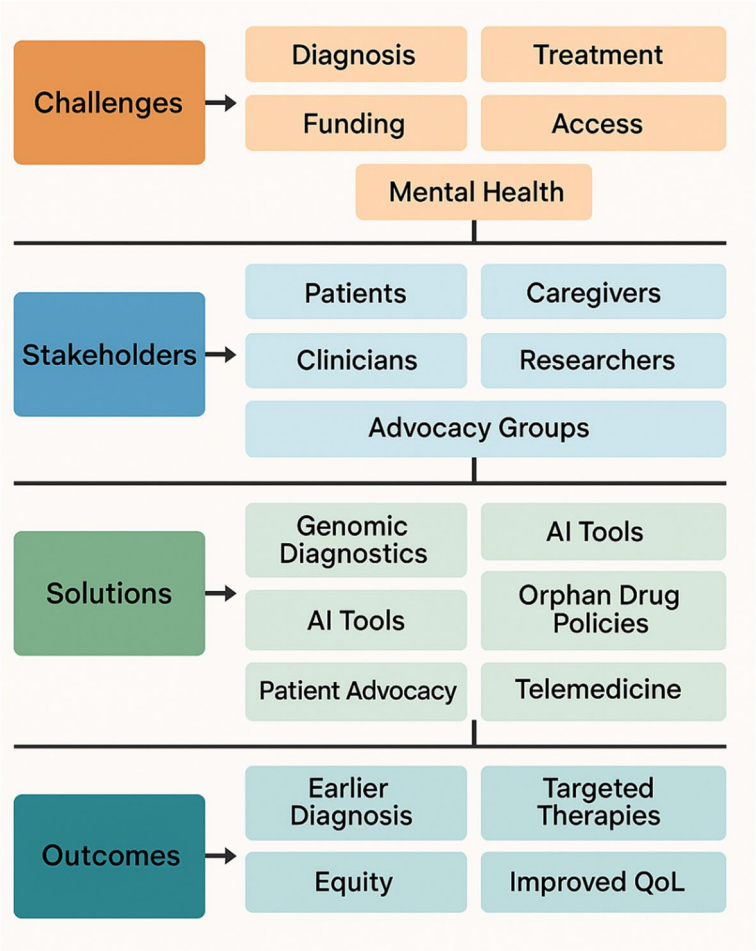

Fig. 1 Conceptual framework of rare disease challenges and solutions

groups can accelerate progress in rare disease research and treatment [9].

Policy and funding improvements

Policy changes are needed to improve rare disease research and treatment accessibility by incentivizing drug development, streamlining regulatory pathways, and ensuring equitable access to care [23]. Addressing inequities in neurological care for underserved groups, including RD patients, requires similar policy interventions [38]. Governments can provide financial incentives, such as tax credits and market exclusivity, to encourage pharmaceutical companies to invest in OD development [22]. Regulatory agencies can expedite the review and approval of ODs, reducing the time it takes for new therapies to reach patients [22]. Increased government and private funding is essential for supporting rare disease research, developing new diagnostic tools, and improving access to treatment [21]. To enhance the impact of such investment, several strategic funding mechanisms can be implemented. Public–private partnerships, involving entities such as the NIH, industry stakeholders, academic institutions, and patient advocacy groups, have proven effective in pooling resources and accelerating research initiatives [55, 56]. Targeted grant programs offered by national bodies like the NIH (USA), NSFC (China), and DFG (Germany) support areas including patient registries, natural history studies, and translational research [55, 57, 58]. International collaborations, such as the EU's E-Rare and the International Rare Diseases Research Consortium (IRDiRC), provide multicenter and cross-border funding frameworks that foster innovation and knowledge sharing [56, 58]. These mechanisms not only expand financial support but also ensure it is effectively aligned with research and clinical priorities.

Funding agencies should prioritize research that addresses unmet needs, promotes innovation, and fosters collaboration among researchers, clinicians, and patient advocacy groups [21]. Private philanthropy can also play a significant role in supporting rare disease research and

providing financial assistance to patients and families [21].

Major global research initiatives have emerged to accelerate rare disease research, diagnosis, and treatment. These include the NIH's National Center for Advancing Translational Sciences (NCATS) Office of Rare Diseases Research, which oversees programs like the Rare Diseases Clinical Research Network and the Genetic and Rare Diseases Information Center (GARD). Other prominent efforts include the International Rare Diseases Research Consortium (IRDiRC), the European Union's E-Rare and European Reference Networks, PCORI's Patient-Powered Research Networks, and hospital-based efforts like the Children's Rare Disease Cohorts [56, 59–62]. These programs support data sharing, international collaboration, patient engagement, and innovative methodologies to address diagnostic and therapeutic gaps.

Many of these initiatives including Horizon Europe, START, RDEA, IRUD, INTENT, and NCRDTRD are increasingly integrating artificial intelligence (AI) and machine learning (ML) technologies for drug repurposing, biomarker identification, patient stratification, and clinical trial optimization. While adoption across global regulatory bodies is still emerging, research networks and pharmaceutical collaborations demonstrate promising progress in incorporating AI to improve the rare disease pipeline [63, 64].

Real-world evidence (RWE) which is derived from patient-reported outcomes (PROs), clinician-reported outcomes, electronic health records (EHRs), and disease/patient registries plays an increasingly vital role in rare disease drug development [65]. It supports clinical trial design, identifies suitable patient populations, and often serves as an external control where traditional randomized controlled trials are not feasible [66]. Regulatory agencies such as the FDA and EMA have issued guidance and frameworks to encourage the integration of RWE into regulatory submissions and approvals, recognizing its value in supplementing limited trial data. Nevertheless, challenges remain in ensuring data quality, standardization, and minimizing bias, especially in decentralized data sources [65–67].

Integrating technology for patient care

Telemedicine and digital health solutions have the potential to transform rare disease care by improving access to specialized expertise, facilitating remote monitoring, and enhancing patient engagement [68]. Telemedicine can enable patients in remote areas to consult with specialists, reducing the need for travel and improving the timeliness of care [68]. Digital health tools, such as mobile apps and wearable devices, can empower patients to track their symptoms, manage their medications, and communicate with their healthcare providers [68].

Patient-centered approaches

Including patients in decision-making is crucial for ensuring that rare disease care is aligned with their needs, preferences, and values [9]. Patient-centered approaches involve actively engaging patients in the development of treatment plans, providing them with comprehensive information about their condition and treatment options, and respecting their autonomy in making healthcare decisions [9]. By empowering patients to take an active role in their care, healthcare providers can improve treatment adherence, enhance patient satisfaction, and promote better outcomes [9]. Improved patient education and community support programs are essential for empowering patients and families affected by rare diseases [10]. Educational resources can provide patients with accurate and up-to-date information about their condition, treatment options, and available support services [10]. Community support programs, such as support groups and online forums, can connect patients and families with others who share similar experiences, providing emotional support, practical advice, and a sense of community [10].

Current research landscape and gaps in therapeutic focus

The current landscape of rare disease research is shaped by a combination of orphan drug initiatives, funding mechanisms, regulatory pathways, and clinical trial activity. However, evidence shows that research and approvals are heavily concentrated in a few therapeutic areas, particularly oncology, leaving critical gaps in others such as neurodegenerative, hematologic, and metabolic disorders.

Orphan drug research initiatives and funding

The FDA's Office of Orphan Products Development (OOPD) has awarded over 700 clinical trial grants since 1983, spanning 18 therapeutic areas and resulting in more than 70 product approvals. Collaborative efforts among stakeholders and adoption of innovative clinical trial designs have contributed significantly to the success of these initiatives [69]. Regulatory bodies such as the FDA and EMA incentivize orphan drug development through financial assistance, special designations, and accelerated approval pathways [70–72]. These include grants, tax credits, and extended market exclusivity under legislation like the Orphan Drug Act [71].

Regulatory approvals and clinical trials

Orphan drug approvals are often based on smaller, non-randomized, and open-label clinical trials, with

regulators showing flexibility in trial design due to the rarity of conditions [71, 73, 74]. Notably, most orphan drug approvals between 2010 and 2019 were for oncology-related indications (25%), followed by infectious diseases (15%) and central nervous system disorders (11%) [74]. Therapeutic areas like neurodegenerative, hematologic, and metabolic conditions receive less than 10% of total approvals and funding, reflecting an imbalance in research attention and investment [74].

Multiple studies have identified critical regulatory hurdles in orphan drug development, particularly due to inconsistent definitions of rare diseases across countries. For instance, the European Union defines rare diseases as affecting fewer than 50 per 100,000 individuals, the United States uses an absolute threshold of fewer than 200,000 people, and China relies on an official list of diseases for classification. These inconsistent prevalence thresholds and qualitative descriptors create barriers to cross-border clinical research and regulatory approval [3, 75, 76]. Experts emphasize the need for international harmonization of rare disease definitions, underpinned by standardized, high-quality epidemiological and pharmacoepidemiological data, to ensure consistent policy implementation, equitable access, and improved global collaboration.

Innovative clinical trial designs for orphan drugs

Clinical trials for orphan drugs face complex challenges that extend beyond the small patient population issue. Many rare diseases have an incomplete natural history, making it difficult to define disease progression or expected outcomes over time [77, 78]. Moreover, there is often an absence of validated clinical endpoints, which limits the ability to assess treatment effectiveness using conventional trial metrics [79]. Methodological limitations, such as difficulties in conducting randomized controlled trials (RCTs), blinding, and placebo allocation, are compounded by ethical concerns and heterogeneity within patient subgroups [80]. Additionally, selection bias is common in rare disease trials, as patients are often recruited from specialized centers, which may not reflect the broader population affected by the condition [79]. These factors pose significant barriers to generating robust, generalizable clinical evidence for regulatory approval. To address these challenges, several adaptive and innovative trial designs have been successfully employed which are illustrated below:

a) Single-arm trials that rely on historical controls when RCTs are infeasible.
b) N-of-one trials where a single patient serves as their own control.
c) Multi-arm adaptive designs that allow for flexible protocol modifications based on interim analyses [77, 79].

The use of surrogate endpoints, patient-reported outcomes (PROs), and biomarker-based assessments has gained acceptance among regulatory agencies such as the FDA and EMA, helping to overcome limitations in standard outcome measures [81]. Regulatory guidance now encourages early engagement with stakeholders, including patient advocacy groups, to incorporate patient-centric perspectives and optimize trial feasibility. Moreover, initiatives such as the FDA's Rare Diseases Program and the EMA's PRIME scheme support tailored trial strategies and expedited review pathways for therapies addressing unmet needs [81]. These alternative approaches demonstrate that, despite inherent limitations, rigorous and impactful clinical research in rare diseases is achievable with innovative design, stakeholder collaboration, and regulatory flexibility [80].

Conclusion

Rare diseases pose significant challenges for individuals, families, and healthcare systems worldwide. These conditions are often difficult to diagnose, lack effective treatments, and are underfunded compared to more common diseases. Addressing these challenges requires a comprehensive and collaborative approach that involves researchers, healthcare professionals, policymakers, and patient advocacy groups.

Key takeaways from this review include the importance of early and accurate diagnosis, the need for increased research funding, the potential of emerging technologies, and the value of patient-centered care. By leveraging advancements in genomics, artificial intelligence, real-world evidence, and precision medicine, we can improve diagnostic accuracy, develop targeted therapies, and personalize treatment plans for individuals with rare diseases. Strengthening collaborative research efforts, promoting policy changes, supporting advocacy groups, and integrating technology into patient care can further enhance outcomes and improve the lives of those affected by rare diseases.

It is imperative that researchers, policymakers, and healthcare professionals work together to address the challenges in rare disease treatment and research. By prioritizing rare diseases, increasing funding, and fostering collaboration, we can make significant progress in improving the lives of millions of individuals and families affected by these conditions. Unlike previous reviews, this study brings together emerging genomic and digital health tools, highlights global disparities, and emphasizes patient-centered and mental health-integrated care

models. It offers actionable insights for advancing rare disease policy, research, and practice in both developed and low-resource settings. A concerted effort is needed to translate scientific discoveries into clinical applications, ensuring that all patients with rare diseases have access to the best possible care.

Authors' contributions
A.C. and V.K. drafted the main manuscript text, conducted the data analysis, and prepared all figures and tables. Both authors reviewed and approved the final manuscript.

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