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Drug Repositioning Strategies to Accelerate Therapeutic Development for Rare Diseases: A Narrative Review

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ABSTRACT. Rare diseases defined as conditions affecting fewer than 1 in 2,000 individuals—collectively affect approximately 300 million people worldwide, yet more than 90% remain without approved therapy. Conventional drug development, with its decade-long timelines, multibillion-dollar costs, and failure rates exceeding 90%, is poorly suited to this population. We conducted a narrative review of the peer-reviewed literature (2019–2025) on drug repositioning for rare diseases, focusing on computational, experimental, clinical/observational, and integrative strategies, regulatory pathways, and illustrative case studies. Sources were identified through targeted searches of PubMed and Google Scholar using combinations of the terms drug repurposing, drug repositioning, rare disease, and orphan drug, supplemented by hand-searching of reference lists. Drug repositioning offers substantial reductions in cost and development time relative to de novo drug discovery by leveraging established safety and pharmacokinetic data. We synthesize evidence across four methodological strategies and illustrate the field's potential and limitations through case studies including thalidomide, sildenafil, and sirolimus. Realizing the full promise of drug repositioning for rare diseases will require stronger data-sharing infrastructure, clearer regulatory pathways for repurposed indications, and sustained collaboration among academia, patient organizations, and industry.

Keywords: drug repositioning, drug repurposing, rare diseases, orphan diseases, computational biology, phenotypic screening, regulatory science.

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1. Introduction

1.1 Definition and Scope of Rare Diseases

Rare diseases, often called orphan diseases, are defined by their low prevalence—typically fewer than 1 in 2,000 individuals in the general population. Approximately 7,000 distinct rare diseases have been identified, collectively affecting around 300 million people worldwide. These conditions display extraordinary clinical diversity, with overlapping symptoms across subtypes, and roughly 80% have a genetic basis (Roessler et al., 2021).

Despite their individual rarity, rare diseases collectively represent a substantial public health burden. Patients frequently endure delayed diagnoses—sometimes spanning years or decades—alongside unclear molecular mechanisms, limited treatment options, and fragmented data. This diagnostic odyssey, compounded by the geographic dispersion of affected individuals, creates significant obstacles for both clinical care and research (Jonker et al., 2024).

1.2 Why Rare Diseases Present Major Therapeutic Challenges

The pathophysiology of rare diseases poses distinct challenges for therapeutic development. Many conditions are characterized by genetic heterogeneity, in which a single disease may arise from mutations in multiple genes with distinct molecular mechanisms; by poorly understood disease biology; by marked phenotypic variability, such that patients sharing a genetic mutation can present very differently; and by the absence of validated biomarkers, which complicates trial design and outcome assessment. Combined with small, geographically dispersed patient populations, these factors render traditional drug development approaches challenging and often economically unviable (Kumar, 2025).

1.3 Traditional Drug Development Limitations in Rare Diseases

The conventional drug development pathway—from target identification through preclinical testing, phased clinical trials, and regulatory approval—typically spans more than a decade and fails roughly 90% of the time. This model, designed for common diseases with large, accessible patient populations, is fundamentally mismatched to rare disease therapeutics.

Three limitations are especially consequential. First, economic disincentives discourage investment: pharmaceutical companies often regard rare disease development as financially unattractive given small patient populations and uncertain returns, and despite incentives such as the US Orphan Drug Act of 1983 (seven years of market exclusivity) and the EU Orphan Regulation of 1999, more than 90% of rare diseases still lack effective therapies (Jonker et al., 2023). Second, clinical trial feasibility is limited: recruiting adequately powered randomized controlled trials is frequently impossible, and multi-country trials introduce added logistical and regulatory complexity. Third, regulatory evidence standards—typically requiring large, placebo-controlled trials with statistically robust endpoints—are difficult to satisfy in small populations (Cortial et al., 2024).

1.4 Introduction to Drug Repositioning

Drug repositioning—identifying new therapeutic uses for existing drugs beyond their original indications—offers an alternative to de novo drug development. Rather than developing new chemical entities, repositioning draws on an existing pharmacopeia with known safety profiles, pharmacokinetic properties, and manufacturing infrastructure. This confers four practical advantages for rare disease research: reduced development time, since established safety data supports faster progression to later-phase testing; lower costs, by avoiding preclinical toxicology and early safety studies; de-risked development, given greater certainty in trial planning; and reliance on existing supply chains.

Roessler et al. (2021) describe drug repurposing as one of the principal opportunities for addressing unmet rare disease need, and the International Rare Diseases Research Consortium (IRDiRC) has

published a dedicated guidebook to advance repurposing efforts in this population (Jonker et al., 2023).

This narrative review aims to (1) synthesize the methodological strategies used in drug repositioning for rare diseases—computational, experimental, clinical/observational, and integrative; (2) describe the regulatory and intellectual property landscape governing repurposed indications; (3) illustrate the field's potential and limitations through representative case studies; and (4) outline future directions, including artificial intelligence, real-world evidence, and adaptive trial designs, that may accelerate progress.

2. The Concept of Drug Repositioning

2.1 Definition

Drug repositioning, synonymous with drug repurposing, refers to the investigation of existing approved drugs for new therapeutic indications. The term also encompasses investigational compounds that completed some phase of clinical development but were never marketed for their original intended use (Roessler et al., 2021).

The underlying concept is not new: many of medicine's most significant therapeutic discoveries have arisen from serendipitous observations of unexpected drug effects. What has changed is the shift toward systematic, hypothesis-driven repositioning, enabled by advances in computational biology, genomics, and data science (Gangwal & Lavecchia, 2025).

2.2 Advantages Compared to De Novo Drug Development

The advantages of repositioning over de novo development are well documented (Table 1).

Table 1. Comparison of de novo drug development and drug repositioning, adapted from cost and timeline estimates reported by Roessler et al. (2021) and Kumar (2025).

Aspect	De Novo Development	Drug Repositioning
Timeline	10–15 years	3–7 years
Cost	$2–3 billion	$50–300 million
Preclinical safety	Extensive animal toxicology	Established human safety data
Phase I trials	Required (healthy volunteers)	Often can be bypassed
Manufacturing	New processes needed	Existing infrastructure
Failure risk	~90%	Substantially lower, though not systematically quantified across indications

Paquot et al. (2024) frame this trade-off succinctly: repurposing exchanges uncertainty about disease biology for greater certainty about the candidate drug—an exchange that is particularly valuable when disease mechanisms are poorly understood but drug properties are well characterized.

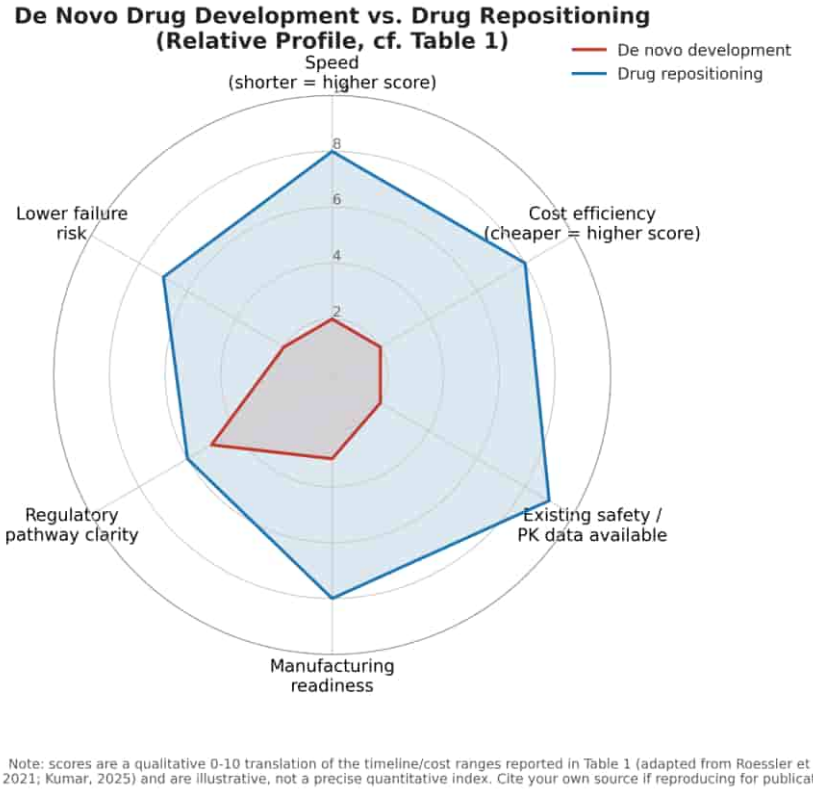


Figure 1. *Relative profile of de novo drug development versus drug repositioning across six practical dimensions (0–10 scale), reflecting the timeline and cost ranges in Table 1. Scores are illustrative expert-elicitation estimates for visualization, not a measured index; sourced data should replace them where cited quantitatively.*

2.3 Scope and Limitations of the Approach

Drug repositioning also carries important limitations. Intellectual property barriers cut both ways: off-patent drugs offer little commercial incentive for investment, while newly patented repurposed uses can, conversely, sustain high prices (Kumar, 2025). Regulatory complexity persists, since new indications may still require de novo clinical trials and pathways for repurposed drugs are not always clearly defined. Payer reluctance is common, as healthcare payers may resist assigning favorable prices to drugs perceived as old. Finally, commercial interest is often limited, with marketing authorization holders showing little appetite for pursuing new rare disease indications for existing products (Jonker et al., 2024).

3. Strategies and Methodologies in Drug Repositioning for Rare Diseases

The four strategy categories discussed below—computational, experimental, clinical/observational, and integrative—were used to organize sources identified through searches of PubMed and Google Scholar (January 2019–June 2025) using combinations of drug repurposing, drug repositioning, rare disease, orphan drug, and strategy-specific terms (phenotypic screening, knowledge graph). Case studies were selected to represent a range of outcomes (successful, partially successful, and unsuccessful) and mechanisms of discovery (serendipitous, computational, and phenotype-driven), rather than through a systematic or exhaustive protocol; as such, this review should be read as a narrative synthesis rather than a systematic review.

3.1 Computational Approaches

Computational methods have become a transformative force in drug repositioning, enabling systematic, data-driven identification of repurposing candidates at scale.

3.1.1 Network-Based Methods

Network-based approaches exploit the interconnected nature of biological systems to predict novel drug–disease associations. By constructing knowledge graphs that integrate diseases, genes, proteins, and drugs, researchers can apply advanced algorithms—including graph neural networks—to identify new therapeutic uses for existing drugs. Wei et al. (2025) trace this evolution from classical machine learning to contemporary graph neural network approaches, noting that such methods are especially valuable in rare diseases, where direct data are sparse but relevant biological relationships can be inferred from broader networks.

3.1.2 Similarity and Phenotype-Matching Methods

Similarity-based approaches identify candidates by matching disease phenotypes to drug effect profiles, on the principle that similar diseases may respond to similar drugs and that drugs sharing a mechanism of action may share therapeutic applications. Gangwal and Lavecchia (2025) review artificial-intelligence-driven advances in repurposing, biomarker discovery, and personalized medicine for rare diseases, and describe hybrid frameworks that integrate transcriptomic and structure-based data to identify candidates for syndromes such as Noonan and LEOPARD syndrome.

3.1.3 Strengths and Limitations

Computational approaches are scalable to large drug and disease databases, can generate testable hypotheses rapidly and inexpensively, and are particularly useful when experimental data are scarce. Their principal limitations are that predictions require experimental validation, that prediction quality depends on the underlying data, that serendipitous or unexpected discoveries may be missed, and that specialized computational expertise is required (Cortial et al., 2024).

3.2 Experimental Approaches

3.2.1 Phenotypic Screening

Phenotypic screening evaluates candidates by their observable effects on cellular or organismal phenotypes rather than on a predefined molecular target—an approach well suited to rare diseases, particularly inherited metabolic disorders, whose mechanisms are often incompletely understood. Paquot et al. (2024) describe how Apteeus has systematically combined phenotypic screening with repurposing to identify therapeutic candidates for ultra-rare patients, arguing that using primary patient cells to model symptom-relevant phenotypes is the most direct and reliable discovery strategy when the causal gene is not linked to a validated target. The DREAMS project applies a

related target-agnostic logic, shifting focus from predefined molecular targets to measurable phenotypic change in cells from patients with muscular disorders (Paquot et al., 2024).

3.2.2 Translational Models

Patient-derived models—including induced pluripotent stem cells (iPSCs), organoids, and primary cell cultures—enable functional testing of repurposed drugs in disease-relevant systems. High-throughput screening in model organisms such as C. elegans has proven useful for identifying candidate treatments for human Mendelian diseases (Hay Mele et al., 2024).

3.3 Clinical and Observational Approaches

3.3.1 Off-Label Observations and Case Reports

Because off-label prescribing is common in the rare disease community, clinical observations—often documented as case reports or case series—constitute a valuable source of repurposing signals. The serendipitous observation that thalidomide dramatically improved erythema nodosum leprosum illustrates this pathway (Kumar, 2025).

3.3.2 Real-World Data and Registries

Patient registries, electronic health records, and clinical databases provide complementary real-world evidence for repurposing. The FDA's CURE ID platform collects such data specifically to support repurposing in rare genetic disorders; this approach contributed to the 2025 FDA approval of chenodeoxycholic acid for cerebrotendinous xanthomatosis (Jonker et al., 2024).

3.4 Integrative and Hybrid Approaches

Researchers increasingly combine computational prediction with experimental validation, clinical observation, and real-world evidence. The SIMPATHIC consortium exemplifies this approach, applying graph-neural-network predictions to identify candidate treatments for rare neurological, neurometabolic, and neuromuscular disorders and subsequently validating these predictions in the laboratory (Wei et al., 2025).

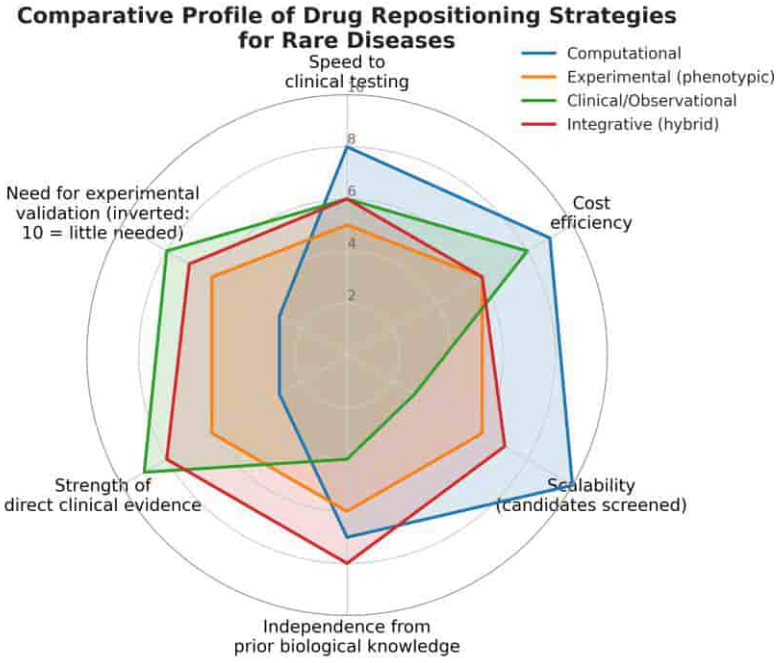


Figure 2. *Comparative profile of the four repositioning strategy families discussed in Section 3, rated on six practical dimensions (0–10 scale). Ratings are illustrative expert-elicitation estimates intended to visualize the qualitative trade-offs described in the text, not a systematic quantitative comparison drawn from the cited literature.*

4. Developmental and Regulatory Pathways

4.1 Orphan Drug Incentives

The US and EU have each established regulatory incentives for rare disease drug development. The US Orphan Drug Act of 1983 provides seven years of market exclusivity, clinical trial tax credits, and a waiver of FDA user fees; the EU Orphan Regulation of 1999 offers ten years of exclusivity, extendable to twelve years with completed pediatric studies (Jonker et al., 2023).

Despite these incentives, the number of FDA orphan-designated approvals rose only from 2 in 1983 to 33 by 2020—modest progress relative to the scale of unmet need. Some observers have also raised concerns that companies exploit orphan provisions for mainstream drugs rather than genuine rare disease needs (Kumar, 2025).

4.2 Regulatory Challenges Specific to Repurposed Drugs

Repurposed drugs face several distinct regulatory hurdles. Generating robust evidence from small patient samples remains, in the words of Cortial et al. (2024), a methodological and logistical challenge. Demonstrating superiority over existing treatment is often difficult given the constraints imposed by disease rarity. Data protection for repurposed medicines is proposed at four years where an unmet medical need and significant clinical benefit are demonstrated. And a lack of alignment—

and poorly timed interaction—between healthcare professionals and regulators creates additional friction (European Medicines Agency, 2022).

The European Medicines Agency's repurposing pilot found that academic teams typically required six months or more to prepare for Scientific Advice, and that most marketing authorization holders showed limited interest in pursuing new rare disease indications (European Medicines Agency, 2022).

4.3 Intellectual Property and Commercial Considerations

Intellectual property considerations shape the repurposing landscape substantially. An analysis of rare disease repurposing patents filed between 2010 and 2023 identified 190 such patents, 75% of which originated from small or medium-sized pharmaceutical companies or university spin-offs (Jonker et al., 2024).

This landscape remains complex: no dedicated patent category exists for repurposing content; patent protection for new uses of existing medicines plays a crucial role in creating viable development pathways; market exclusivity does not appear to be a primary motivator for nonprofit rare disease organizations; and excessive patent protection can, paradoxically, undermine successful repurposing (Kumar, 2025).

5. Case Studies in Rare Disease Drug Repositioning

5.1 Thalidomide

Thalidomide offers one of the most dramatic examples of drug repositioning in medical history. Marketed in the 1950s as a sedative and antiemetic for pregnant women, it caused severe birth defects and was withdrawn from the market.

Decades later, a physician in Jerusalem observed, through compassionate use, that thalidomide dramatically improved erythema nodosum leprosum (ENL), a rare complication of leprosy. Subsequent research showed that thalidomide acts by modulating immune response and inhibiting angiogenesis. The FDA approved thalidomide for ENL in 1998 and for multiple myeloma, a rare blood cancer, in 2006 (Kumar, 2025).

This case illustrates three recurring lessons: serendipitous clinical observation can yield major therapeutic breakthroughs; drugs with concerning safety profiles in one context may be used safely in another with appropriate risk management; and repositioning can convert a withdrawn or problematic drug into a valuable therapeutic tool.

5.2 Sildenafil

Sildenafil, originally developed for angina pectoris, was famously repurposed for erectile dysfunction and, subsequently, for pulmonary arterial hypertension (PAH), a rare and life-threatening condition.

More recently, sildenafil has shown promise in mitochondrial disease. Using iPSC-based drug discovery, researchers screened a compound library and identified sildenafil as a candidate for Leigh syndrome, a severe mitochondrial disorder. Chronic off-label, compassionate-use treatment of six patients showed good tolerability and clear clinical improvement; sildenafil has since received Orphan Drug Designation for Leigh syndrome and is now under evaluation in a pivotal Phase III trial (Hay Mele et al., 2024).

5.3 Sirolimus (Rapamycin)

Originally developed to prevent organ rejection after kidney transplantation, sirolimus has been repurposed for several rare genetic syndromes. By inhibiting the mTOR pathway, it reduces the abnormal cell growth that drives these disorders and has shown efficacy in congenital vascular malformations. A Radboudumc team won the Drug Repurposing Venture Challenge with a plan to make sirolimus formally available for this indication (Jonker et al., 2024).

5.4 An Unsuccessful Attempt: General Lessons from Failed Repurposing

Not all repurposing efforts succeed, and understanding failure is as instructive as celebrating success. Common causes include a lack of efficacy in the new indication despite encouraging preclinical data; unexpected toxicity when a drug is used in a different population or at a different dose; regulatory hurdles that cannot be resolved with available evidence; and commercial barriers that prevent investment in the clinical trials needed to confirm efficacy. Rituximab's evaluation for graft-versus-host disease, for example, was ultimately discontinued after toxicity concerns emerged (see Table 2).

As Kumar (2025) observes, although the number of novel rare disease treatments has grown substantially over recent decades, many conditions still lack an FDA-approved therapy; even scientifically promising candidates remain constrained by limited attention from for-profit pharmaceutical developers (Jonker et al., 2024).

Table 2. Illustrative case studies of drug repositioning in rare diseases.

Drug	Target Rare Disease	Original Use	Outcome	Year
Thalidomide	Multiple myeloma	Nausea in pregnancy	Approved (FDA)	1998/2006
Sildenafil	Pulmonary hypertension	Angina	Approved (FDA)	2005
Clozapine	Treatment-resistant schizophrenia*	Antipsychotic	Approved (restricted)	1989
Rituximab	Graft-versus-host disease	Cancer (lymphoma)	Discontinued (toxicity)	2008

** Not classified as a rare disease under standard prevalence criteria; retained here for methodological illustration and flagged for the authors to confirm inclusion criteria.*

5.5 Cross-Cutting Lessons

Four themes recur across successful and unsuccessful cases. Patient advocacy and collaboration are critical: nonprofit engagement, leveraging registries and direct outreach, has accelerated trial enrollment in several programs (Nijim et al., 2025). Early regulatory engagement matters: seeking scientific advice early and sharing clinical observations promptly smooths the development pathway (European Medicines Agency, 2022). Converging lines of evidence strengthen the case for repurposing, since computational prediction, experimental validation, and clinical observation are most persuasive in combination. And public–private collaboration accelerates progress, as innovation platforms, real-world data initiatives, and AI tools tend to be most effective when developed jointly across sectors (Jonker et al., 2023).

6. Challenges and Limitations Specific to Rare Diseases

6.1 Biological Uncertainties

Many rare diseases have poorly characterized pathophysiology, with unclear molecular pathways and an incomplete understanding of disease mechanisms. This uncertainty complicates both target selection and the interpretation of drug effects. Paquot et al. (2024) frame the core difficulty as one of insufficient accessible knowledge—about both the drug and the disease—needed to de-risk development in a new indication.

6.2 Small Patient Numbers and Trial Design Difficulties

Small, dispersed patient populations create substantial trial-design challenges: insufficient statistical power for conventional randomized trials, difficulty recruiting adequate samples, clinical heterogeneity that complicates outcome measurement, and a scarcity of validated outcome assessments. Cortial et al. (2024) summarize these as a combination of small, geographically dispersed populations, poorly developed endpoints, insufficient patient data, and inappropriate control groups.

6.3 Data and Evidence Gaps

Rare disease research is further constrained by fragmented patient data across institutions and countries, limited natural history data to inform trial design, an absence of validated biomarkers for many conditions, and publication bias toward positive results. Together, these gaps complicate both the identification of repurposing candidates and the generation of evidence sufficient for regulatory approval (Gangwal & Lavecchia, 2025).

6.4 Commercial and Financial Hurdles

Commercial barriers include limited financial incentive, given that companies often view rare disease repurposing as a suboptimal investment; payer reluctance to assign favorable prices to repurposed drugs; intellectual property challenges for off-patent compounds; and development

costs that are high relative to likely returns. Nijim et al. (2025) show that nonprofit engagement can offset some of these barriers by leveraging patient advocacy networks and registries to accelerate enrollment and improve the representativeness of study populations.

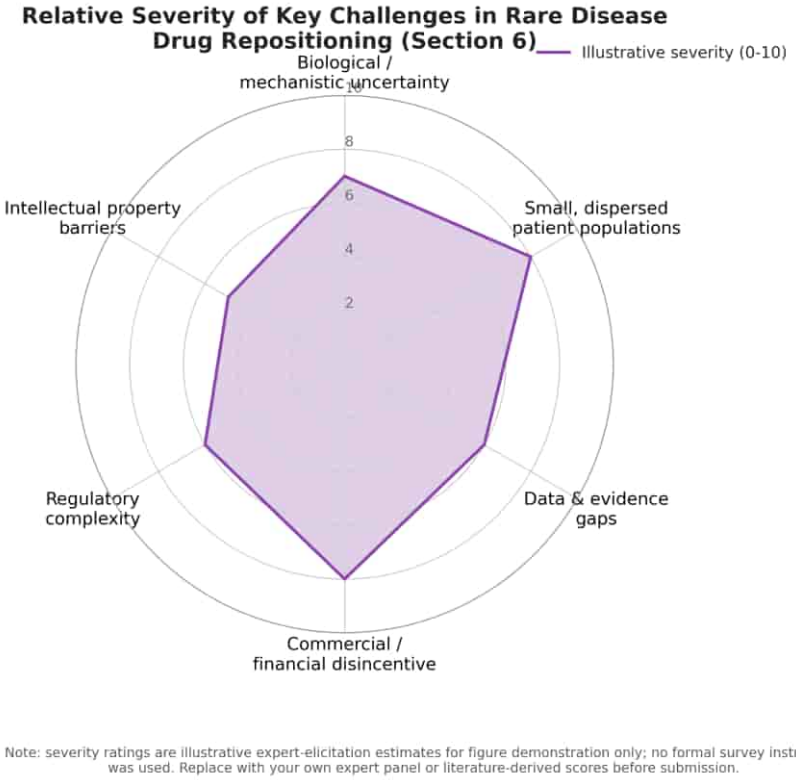


Figure 3. *Relative severity of the key challenges discussed in Section 6 (0–10 scale). Ratings are illustrative estimates for figure demonstration only; no formal expert-panel survey was conducted. Replace with literature-derived or panel-sourced scores before submission.*

6.5 Limitations of This Review

As a narrative rather than systematic review, this synthesis does not follow a pre-registered protocol, and source selection—while guided by the search strategy described in Section 3—was not exhaustive and may be subject to selection bias. The literature reviewed is predominantly in English and originates largely from North American and European sources, which may underrepresent repurposing initiatives elsewhere. Quantitative comparisons (cost and timeline estimates in Table 1) draw on a limited number of published estimates and should be interpreted as indicative rather than precise.

7. Future Perspectives and Opportunities

7.1 Precision Medicine and Patient Stratification

Advances in genomics and molecular biology increasingly allow precise characterization of rare diseases. Patient stratification—identifying subgroups most likely to respond to a given therapy—can improve the efficiency of repurposing efforts. Integrating multi-omics data (genomics, transcriptomics, proteomics, metabolomics) with clinical information supports more targeted repurposing; Gangwal and Lavecchia (2025) describe AI-driven advances in biomarker discovery as

central to overcoming the data limitations that have historically constrained rare disease drug discovery.

7.2 Real-World Evidence and Adaptive Trial Designs

Real-world evidence is an increasingly valuable complement to traditional trial data; platforms such as CURE ID collect real-world treatment data specifically to support repurposing in rare genetic disorders (Jonker et al., 2024). Adaptive designs, including basket trials that evaluate multiple rare disease indications within a single framework, can improve trial efficiency and relevance, accelerate patient access to candidate treatments, and support better-informed clinical decisions (Cortial et al., 2024).

7.3 Ethical and Economic Considerations

Several ethical and economic questions merit attention as repurposing efforts scale: ensuring access and affordability for patients who need repurposed drugs; addressing regional and population-level disparities in rare disease research and treatment; developing sustainable business models that do not rely on excessive pricing; and meaningfully engaging patients and families throughout the repurposing process. The IRDiRC Drug Repurposing Guidebook identifies patient engagement as a defining feature of successful repurposing initiatives (Jonker et al., 2023).

8. Conclusions

Drug repositioning offers a credible strategy for accelerating therapeutic development in rare diseases, reducing cost, time, and developmental risk relative to de novo discovery. The convergence of computational methods—network-based prediction, artificial intelligence, knowledge graphs—with experimental strategies such as phenotypic screening and patient-derived models is expanding what repurposing can achieve, while collaborative frameworks spanning academia, nonprofits, and industry are demonstrating that systematic repurposing is feasible even without traditional commercial incentives.

Progress nonetheless depends on addressing the structural barriers documented throughout this review: biological uncertainty, small and dispersed patient populations, persistent data gaps, and limited commercial interest. For the field to advance, three groups have distinct roles to play. Academic and clinical researchers should prioritize systematic documentation of off-label observations and early data sharing. Regulators should continue to clarify evidentiary pathways for repurposed indications, building on pilots such as the EMA's repurposing initiative. And industry and patient organizations should expand collaborative funding models that do not depend solely on patent-driven exclusivity. As the IRDiRC guidebook concludes, sharing clinical observations, engaging regulators early, and sustaining public–private collaboration remain the clearest path to bringing effective repurposed treatments to the millions of patients living with rare diseases (Jonker et al., 2023).

Declarations

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Authors' Contributions

KY: Conceptualization, investigation, data curation, and writing – original draft. **NS:** Methodology, validation, writing – review & editing, and project administration. **WG:** Resources, visualization, and writing – review & editing. All authors contributed to the final version and approved the manuscript for submission

Availability of Data and Materials

All data supporting the findings are included within the article and its tables. The full evidence table is available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflict of interest.

Consent for Publication

Not applicable.

Ethical Considerations

This study As a Narrative review of published studies, no primary data collection from human participants was conducted.

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Artificial Intelligence Disclosure

During the preparation of this narrative review, the authors used Python (version 3.x) with the Matplotlib library solely to generate the illustrative figures (Figures 1, 2, and 3). Additionally, the authors used Claude (Anthropic), a large language model, exclusively for language polishing, grammar correction, and clarity enhancement during the revision process. No artificial intelligence tools were used for data analysis, conceptualization, literature search, or the generation of scientific content. After using these tools, the authors carefully reviewed and edited the final manuscript and take full responsibility for the integrity, accuracy, and final content of this publication.

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