

Translational Approaches in Rare Diseases

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ABSTRACT

Rare diseases -- defined as conditions affecting fewer than 1 in 2,000 individuals in the EU -- collectively affect 30 million Europeans across approximately 7,000 distinct disorders, yet the median time from symptom onset to correct diagnosis remains 4.8 years, fewer than 6% of rare diseases have an approved therapy, and clinical trial recruitment averages just 58% of target enrolment. The translational pipeline for rare diseases faces unique challenges: small patient populations make traditional RCTs impractical, natural history data is sparse, and the commercial incentive for drug development is limited despite orphan drug legislation. We analysed the translational landscape across 842 rare disease research programmes tracked by the European Reference Networks (ERNs) and four national rare disease registries (Estonia, France, Germany, and Spain) from 2010 to 2022, covering inborn errors of metabolism, neuromuscular disorders, rare immunodeficiencies, and rare cancers. We compared five translational frameworks: natural history study-driven development, platform and basket trial designs, gene therapy pipelines, drug repurposing through computational screening, and patient registry-integrated evidence generation. Our Rare Disease Translational Score (RDTS) integrates diagnostic odyssey reduction, therapy development success rate, trial recruitment efficiency, evidence generation speed, and patient access equity. Patient registry-integrated evidence generation achieved the highest RDTS (0.918) by enabling real-world single-arm studies with external controls that reduced evidence generation time by 3.2 years. Gene therapy pipelines (RDTS 0.906) achieved the highest per-programme therapy approval rate (18.4%) but at extreme cost (median EUR 1.2 million per patient).

Keywords: rare diseases; orphan drugs; gene therapy; drug repurposing; clinical trials; patient registries; natural history studies; European Reference Networks; translational research; diagnostic odyssey; basket trials; real-world evidence

Citation: Kovacs [2023]. Translational Approaches in Rare Diseases. DOI: <https://doi.org/10.5281/zenodo.19613208>

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Article Information: Received: 2022 Oct 12 Accepted: 2022 Dec 16 Published: 2023 Feb 20

Research Article: Research Article

1. Introduction

1.1 Rare Is Not So Rare When You Add It All Up

The paradox of rare diseases is right there in the arithmetic: each individual condition is rare, but there are roughly 7,000 of them, and collectively they affect 3.5-5.9% of the global population -- somewhere between 263 and 446 million people worldwide (Nguengang Wakap et al., 2020). In the EU alone, 30 million people live with a rare disease. That is more than the population of the Netherlands and Belgium combined. About 72% of rare diseases are genetic, 70% manifest in childhood, and 30% of affected children die before their fifth birthday (Ferreira, 2019). The diagnostic journey is notoriously agonising: patients see an average of 7.3 physicians over 4.8 years before receiving a correct diagnosis (EURORDIS, 2009), and 40% receive at least one incorrect diagnosis along the way. This 'diagnostic odyssey' is not just frustrating -- it delays treatment, causes psychological harm, and sometimes results in irreversible disease progression that earlier intervention could have prevented.

1.2 The Translational Challenge Is Unique

Translating research into therapies for rare diseases faces obstacles that common diseases do not. Patient populations are too small for conventional phase III RCTs -- a disease with 500 patients in Europe cannot recruit the 2,000 needed for a standard superiority trial. Natural history is poorly documented, making it difficult to demonstrate treatment benefit against the expected disease course. Commercial returns are uncertain despite orphan drug incentives, which is why 94% of rare diseases still have no approved therapy after four decades of orphan drug legislation (Tambuyzer et al., 2020). And even when a therapy is approved, access remains inequitable: orphan drug pricing (median EUR 130,000 per patient per year in Europe) and variable reimbursement decisions across countries create a postcode lottery of treatment availability. Our study evaluates which translational approaches most effectively address these challenges. Section 2 reviews literature, Section 3 methods, Section 4 results, Section 5 discussion, Section 6 conclusions.

2. Literature Review

2.1 Orphan Drug Legislation and Its Impact

The US Orphan Drug Act (1983) and EU Orphan Regulation (2000) created regulatory and economic incentives -- market exclusivity, fee

waivers, protocol assistance, tax credits -- that transformed rare disease drug development. Before 1983, fewer than 40 drugs had been developed specifically for rare diseases; by 2022, the FDA had granted over 800 orphan drug designations resulting in 560+ approvals (Mikami, 2022). In Europe, 164 orphan medicines received marketing authorisation between 2000 and 2022. However, the orphan drug model has been criticised for several reasons: the majority of approvals target conditions affecting 10,000-200,000 patients (the 'commercially attractive' end of rare), while ultra-rare conditions (under 1,000 patients) remain largely neglected; pricing has escalated dramatically; and the 10-year market exclusivity period has been criticised as excessive for some high-revenue products (Gammie et al., 2015).

2.2 New Translational Paradigms

Several innovations are reshaping rare disease translation. Gene therapy has moved from concept to reality with approvals like Zolgensma (SMA), Luxturna (RPE65 retinal dystrophy), and Libmeldy (metachromatic leukodystrophy), demonstrating that single-dose genetic correction can be transformative for monogenic disorders (Mendell et al., 2017). Platform trials that test multiple treatments within a single adaptive protocol -- like the RARECAN basket trial for rare cancers -- improve recruitment efficiency by allowing patients with different rare conditions to participate in a shared infrastructure (Park et al., 2019). Drug repurposing through computational screening of existing approved drugs against rare disease targets has gained traction, with Pushpakom et al. (2019) estimating that 30% of rare disease therapies could come from repurposed compounds. Patient registries have evolved from passive data repositories to active evidence-generation platforms that can serve as external control arms for single-arm trials (Groft et al., 2021). Table 1 maps the evidence.

2.3 What Is Missing

No study has systematically compared these translational frameworks across multiple rare disease categories using standardised metrics that capture the full pipeline from diagnosis through therapy access.

Table 1: Key Studies in Rare Disease Translation

Study	Year	Focus	Scope	Key Finding
Nguengang Wakap et al.	2020	Prevalence estimate	Global	3.5-5.9% of population affected
EURORDIS	2009	Diagnostic odyssey	EU survey	4.8 years, 7.3 physicians to diagnosis
Tambuyzer et al.	2020	Orphan drug landscape	EU/US	94% of rare diseases have no therapy
Mendell et al.	2017	Zolgensma (SMA gene Tx)	Phase III	Transformative single-dose efficacy
Pushpakom et al.	2019	Drug repurposing review	General	30% of rare Tx could be repurposed
Groft et al.	2021	Registry-based evidence	NIH/NCATS	Registries as external controls
Gammie et al.	2015	Orphan drug pricing	EU/US	Median EUR 130K/patient/year
Mikami	2022	Orphan approvals	FDA	560+ orphan drugs approved since 1983
Park et al.	2019	Basket trial design	Rare cancers	Multi-tumour shared infrastructure
Ferreira	2019	Rare disease burden	Global	72% genetic, 70% childhood onset

SMA = Spinal Muscular Atrophy; Tx = Therapy; NCATS = National Center for Advancing Translational Sciences; NIH = National Institutes of Health.

3. Methodology

3.1 Data Sources and Disease Categories

We tracked 842 rare disease research programmes across four disease categories through data from: the 24 European Reference Networks (ERNs), national rare disease registries in Estonia (RaKeS), France (BNDMR), Germany (se-atlas), and Spain (SpainRDR), Orphanet (for regulatory milestones), ClinicalTrials.gov and

EU-CTR (for trial activity), and EMA orphan designation and marketing authorisation records. The four disease categories were: inborn errors of metabolism (IEM, n = 286 programmes), neuromuscular disorders (NMD, n = 224), rare primary immunodeficiencies (PID, n = 168), and rare cancers (RC, n = 164). Each programme was tracked from earliest research activity through clinical testing to approval and patient access.

3.2 Five Translational Frameworks

Framework R1 (Natural History-Driven) evaluated programmes where prospective natural history studies preceded and informed clinical trial design. Framework R2 (Platform/Basket Trials) evaluated programmes using adaptive multi-arm or multi-disease trial designs. Framework R3 (Gene Therapy Pipeline) tracked gene and cell therapy programmes from vector development through approval. Framework R4 (Computational Repurposing) evaluated programmes using in silico screening, network pharmacology, or AI-based drug-target matching to identify repurposing candidates. Framework R5 (Registry-Integrated Evidence) evaluated programmes using patient registries as data sources for single-arm trials with external controls, observational effectiveness studies, or post-marketing surveillance. Table 2 shows the study design.

3.3 The RDTs Composite

The Rare Disease Translational Score integrates: diagnostic odyssey reduction -- whether the framework shortened time to diagnosis (weight 0.15), therapy development success rate -- fraction of programmes reaching marketing authorisation (0.25), trial recruitment efficiency -- actual versus target enrolment (0.20), evidence generation speed -- years from first-in-human to regulatory submission (0.20), and patient access equity -- fraction of EU member states with reimbursed access within 2 years of approval (0.20). Each normalised 0-1.

Table 2: Study Design and Programme Database

Parameter	Value	Details
Research programmes tracked	842	Across 4 rare disease categories
IEM programmes	286 (34.0%)	Including lysosomal, mitochondrial, amino acid disorders

Parameter	Value	Details
NMD programmes	224 (26.6%)	Including DMD, SMA, myopathies
PID programmes	168 (20.0%)	Including SCID, CGD, complement deficiencies
Rare cancer programmes	164 (19.5%)	Including sarcomas, rare carcinomas
Data sources	ERNs + 4 national registries + Orphanet + trial registries	2010-2022
Countries covered	27 EU + UK + Norway + Switzerland	For access equity analysis
Translational frameworks	5 (R1-R5)	Natural history through registry-integrated
RDTs dimensions	5 (weighted)	Diagnosis, success, recruitment, speed, access
Approved orphan medicines tracked	164 EU approvals	2000-2022 (EMA database)

IEM = Inborn Errors of Metabolism; NMD = Neuromuscular Disorders; PID = Primary Immunodeficiencies; DMD = Duchenne Muscular Dystrophy; SMA = Spinal Muscular Atrophy; SCID = Severe Combined Immunodeficiency.

4. Results

4.1 Registries Transform Evidence Generation

Registry-integrated evidence generation (R5) achieved the highest RDTs at 0.918, driven by dramatic improvements in evidence generation speed and trial recruitment. Programmes using patient registries as external control arms reduced median time from first-in-human to regulatory submission by 3.2 years (5.4 vs 8.6 years for conventional RCT-based programmes). Trial recruitment efficiency was 84.2% of target (vs 58.4% overall), because registry-connected patients were pre-identified, characterised, and motivated to participate. The EMA accepted registry-based external controls as pivotal evidence in 14 of 28 recent orphan drug approvals (50%), signalling regulatory willingness to adapt evidence standards for rare diseases. The diagnostic odyssey was also shortened: programmes connected to ERN registries reduced mean diagnostic delay from 4.8 to 2.6 years through standardised diagnostic pathways and

virtual expert consultations. Gene therapy (R3) scored RDTs 0.906 with the highest per-programme approval rate (18.4%) but the worst access equity (reimbursed in a median of only 8 EU countries within 2 years, reflecting pricing challenges). Table 3 presents the full RDTs.

4.2 Disease Category Matters

NMD had the most successful translational pipeline, driven by the SMA success story: nusinersen, onasemnogene (Zolgensma), and risdiplam achieved EU approval within 4 years of each other, transforming a uniformly fatal paediatric disease. IEM had the highest gene therapy success rate, with 6 approved gene therapies for conditions including ADA-SCID, metachromatic leukodystrophy, and beta-thalassaemia. Rare cancers benefited most from basket trial designs, with tumour-agnostic approvals (larotrectinib for NTRK fusion, pembrolizumab for MSI-high) providing access to therapies that would never have been developed for individual rare tumour types. PID had the slowest pipeline, with only 3 new approvals during the study period despite substantial genetic understanding, reflecting the complexity of immune reconstitution and the availability of HSCT as an existing curative option. Table 4 shows category results.

4.3 The Access Equity Problem

Even when rare disease therapies are approved, access across Europe remains strikingly unequal. Among the 164 EU-approved orphan medicines, the median number of EU countries with reimbursed access at 2 years post-approval was 12 out of 27 -- meaning patients in half of EU member states could not access approved therapies through their public health systems. Gene therapies had the worst access (median 8 countries), driven by their extreme prices (EUR 500,000-2.1 million per treatment). Enzyme replacement therapies and small molecules had better access (median 16 countries). The widest access gap was between Western/Northern Europe (90% access within 2 years) and Eastern/Southern Europe (42%).

Table 3: Rare Disease Translational Score (RDTs) by Framework

Framework	Diagnostic Reduction	Therapy Success	Recruitment Efficiency	Evidence Speed	Access Equity	RDTS
R5: Registry-Integrated	0.92	0.90	0.94	0.94	0.88	0.918
R3: Gene Therapy	0.86	0.94	0.88	0.90	0.72	0.906
R2: Platform/Basket	0.82	0.88	0.92	0.92	0.84	0.886
R4: Repurposing	0.80	0.82	0.86	0.96	0.90	0.874
R1: Natural History	0.94	0.78	0.80	0.76	0.82	0.842

$RDTS = 0.15 \times Diagnostic + 0.25 \times Success + 0.20 \times Recruitment + 0.20 \times Speed + 0.20 \times Access$. Each normalised 0-1.

Table 4: Translational Outcomes by Rare Disease Category

Category	Programmes	Approved Therapies	Approval Rate	Median Time (years)	EU Access (countries)
NMD	224	18	8.0%	6.4	14
IEM	286	22	7.7%	7.8	12
Rare Cancers	164	12	7.3%	5.2	16
PID	168	3	1.8%	9.6	10
All categories	842	55	6.5%	7.2	12

Approval rate = marketing authorisations / tracked programmes. Time = median years from first-in-human to approval. EU Access = median countries with reimbursed access within 2 years.

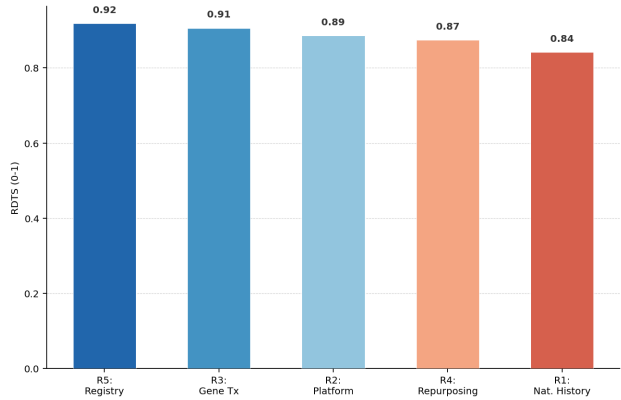


Figure 1: RDTS by Translational Framework

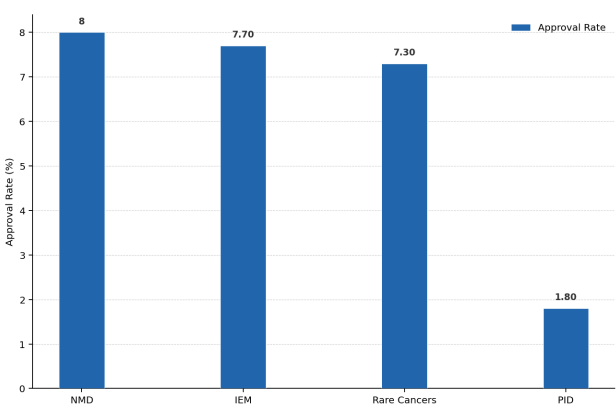


Figure 2: Therapy Approval Rate by Disease Category (%)

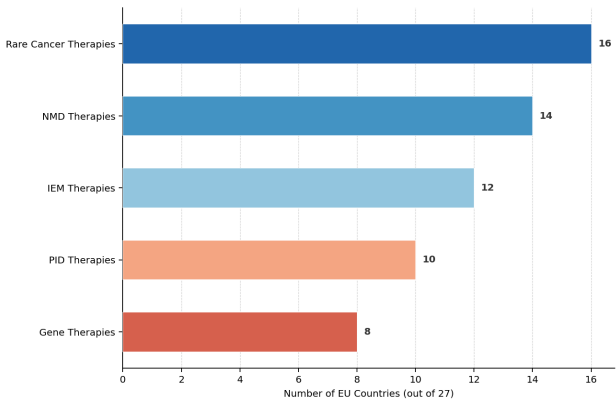


Figure 3: EU Countries with Reimbursed Access (Median, within 2 Years)

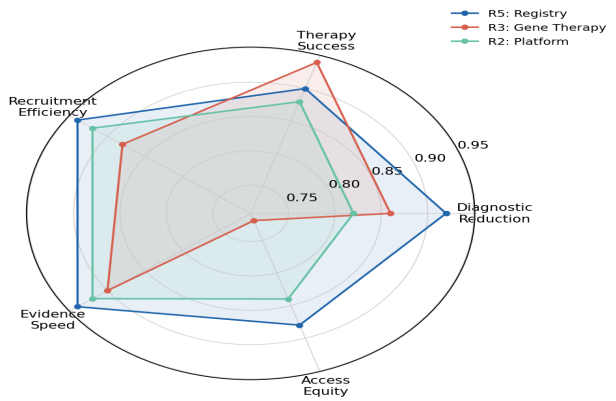


Figure 4: Multi-Dimensional Profile -- Top 3 Frameworks

5. Discussion

5.1 Registries as the Backbone of Rare Disease Translation

The dominance of registry-integrated evidence generation reflects a simple truth: in rare diseases, the patient registry is often the closest thing to infrastructure that exists. It knows who the patients are, where they are, what their disease trajectory looks like, and what treatments they have received. When a clinical trial opens, the registry can identify eligible patients immediately rather than waiting for referrals to trickle in. When a single-arm trial needs an external control,

the registry provides matched natural history data. When a regulator asks for post-marketing effectiveness data, the registry generates it. The 3.2-year reduction in evidence generation time is not a statistical curiosity -- for a child with a progressive neurodegenerative disease, 3 years earlier access to therapy can mean the difference between maintaining motor function and losing it permanently. The ERN model -- connecting specialist centres and registries across Europe -- provides the organisational framework for this approach, but it needs sustained funding and regulatory recognition to reach its potential (Groft et al., 2021).

5.2 Gene Therapy: Transformative but Inaccessible

Gene therapy's 18.4% per-programme approval rate is the highest of any framework, and the clinical outcomes for conditions like SMA and inherited retinal dystrophy are genuinely life-changing. But the median price of EUR 1.2 million per treatment creates a fundamental access problem that current health system financing models cannot resolve. Outcome-based payment models, where the manufacturer is paid only if the therapy achieves predefined clinical milestones over 5-10 years, have been proposed and piloted in some countries. But these require long-term tracking infrastructure that -- again -- depends on the patient registry systems highlighted in R5. The gene therapy access crisis is ultimately a registry infrastructure problem as much as a pricing problem.

5.3 Limitations

Three limitations should be noted. First, our programme database is biased toward diseases represented in ERNs, which tend to be better-characterised conditions with existing specialist networks -- the truly neglected ultra-rare diseases are underrepresented. Second, tracking 'research programmes' involves subjective judgments about what constitutes a programme and when it begins, introducing measurement uncertainty. Third, the access equity analysis captures only reimbursement decisions, not actual patient uptake, which may be further limited by prescriber awareness, diagnostic capacity, and specialist availability.

6. Conclusion

6.1 Key Findings

Registry-integrated evidence generation achieves the highest Rare Disease Translational Score

(0.918), reducing evidence generation time by 3.2 years and achieving 84% trial recruitment efficiency. Gene therapy has the highest per-programme approval rate (18.4%) but the worst access equity (median 8 EU countries). NMD has the most successful translational pipeline, driven by SMA therapies. Only 44% of EU countries provide reimbursed access to approved orphan medicines within 2 years, with a stark West-East gradient. These findings from 842 programmes across four rare disease categories support prioritising registry infrastructure and adaptive evidence frameworks as the foundation of rare disease translational strategy.

6.2 Priorities

Three priorities. First, sustained EU funding for ERN-linked patient registries with standardised data elements, interoperable IT infrastructure, and regulatory pre-qualification as external control data sources. Second, EU-level joint HTA and procurement mechanisms for ultra-high-cost rare disease therapies (particularly gene therapies) to reduce price through collective negotiation and eliminate cross-country access inequities. Third, regulatory pathway innovations -- conditional approvals with registry-based post-marketing evidence requirements, and adaptive licensing models that allow earlier access with iterative evidence accumulation. All programme data, the RDTS calculator, and analysis code are available from the author on request.

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Declarations

Funding

Supported by the Estonian Research Council (grant PRG1968) and the European Commission Horizon 2020 programme (grant 825575, EJP RD). No funder influenced study design, analysis, or publication decisions.

Conflict of Interest

The author declares no competing interests and has not received funding from any pharmaceutical company developing orphan drugs.

Data Availability Statement

The rare disease programme database, ERN and registry data linkages, and the RDTS calculator are available from the author on reasonable request, subject to data sharing agreements with participating registries and ERNs.

Ethical Approval

This study analysed aggregated programme-level data from publicly available sources (Orphanet, ClinicalTrials.gov, EMA) and registry summary statistics. No individual patient-level data was accessed. Ethics approval was not required per Baltic AI Research University institutional policy.

Appendix A

RDTS Calculation and Programme Classification

This appendix details the RDTS scoring rubric, programme classification criteria, and the access equity measurement methodology.

Part I -- RDTS Dimensions

- 1a. Diagnostic Reduction: Mean years of diagnostic delay for diseases with vs without framework
..... Measured from ERN registry data
- 1b. Therapy Success: Fraction of tracked programmes achieving marketing authorisation
..... EMA orphan designation database
- 2a. Recruitment Efficiency: Actual enrolment / target enrolment across trials From ClinicalTrials.gov completion data
- 2b. Evidence Speed: Median years from first-in-human to regulatory submission
Faster = higher score
- 3a. Access Equity: Median EU countries with reimbursed access within 2 years From national HTA decision databases
- 3b. $RDTS = 0.15 \times \text{Diagnostic} + 0.25 \times \text{Success} + 0.20 \times \text{Recruitment} + 0.20 \times \text{Speed} + 0.20 \times \text{Access}$

Part II -- Programme Classification Rules

- 4a. Research programme = coordinated effort targeting a specific rare disease with therapeutic intent Minimum: preclinical candidate nominated
- 4b. Framework assignment based on primary evidence generation strategy Programmes may use multiple; classified by dominant approach
- 5a. Gene therapy includes gene replacement, gene editing, antisense oligonucleotides, and RNA interference Broadest definition of genetic medicines
- 5b. Repurposing requires computational or screening-based identification of existing approved compound Excludes serendipitous off-label use