

Intrinsic and Extrinsic Challenges in Rare Diseases: Connecting Global Collaboration with National Health-System Realities

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matters-arising

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Abstract

Background Rare diseases share challenges arising from low individual prevalence, biological complexity, limited knowledge, small and geographically dispersed patient populations, and restricted incentives for developing diagnostics and treatments. These intrinsic obstacles justify international cooperation, shared data, common scientific standards and multinational research. However, affected people also face extrinsic problems created by the country and health system in which they live.

Main body Fragmented care, weak referral pathways, unequal access to specialists and diagnostic technologies, incomplete information systems, financial barriers, limited regulatory incentives and discontinuous policies may be as consequential as rarity itself. These constraints are particularly visible in low- and middle-income countries but vary between and within nations. Global programmes therefore cannot be transferred as uniform models. International collaboration should address shared scientific problems while reinforcing national capacity. Each country needs a comprehensive rare-disease plan consistent with its epidemiological, social, economic and institutional reality. A layered registry can provide an essential foundation for that plan by distinguishing confirmed rare diseases, clinically supported suspicions and unresolved atypical or multisystem conditions. The registry should support planning, accountability and measurable improvement, while remaining an instrument within an integrated strategy that also addresses referral, diagnosis, care, research, treatment access, financing and evaluation.

Conclusions Recognising the intrinsic–extrinsic distinction can help connect global knowledge with locally effective action. National policies must look beyond confirmed diagnoses and include suspected and undiagnosed conditions, especially where diagnostic confirmation is difficult.

Background

Rare diseases are individually uncommon but collectively represent a substantial public-health burden. Current estimates based on the Orphanet database suggest that rare diseases affect approximately 3.5–5.9% of the world population, excluding rare cancers, infectious diseases and poisonings [1]. Considered together, people affected by these thousands of conditions may constitute the largest collective of health minorities whose needs have yet to be adequately addressed. Their combined demand for diagnosis, care, treatment and social support is sufficiently large to warrant priority on national and international public-policy agendas. Their diversity is striking: thousands of conditions have been described, and the boundaries of the field continue to evolve as genomic and phenotypic knowledge improves [2, 3]. Despite this heterogeneity, affected people repeatedly encounter delayed diagnosis, scarcity of expertise, fragmented care, limited therapeutic options and major social and economic consequences.

The international rare-disease community has appropriately responded by promoting networks, registries, common data standards, multinational research and shared regulatory approaches. Organisations and initiatives such as Orphanet, the International Rare Diseases Research Consortium

(IRDiRC), the Undiagnosed Diseases Network International (UDNI), European Reference Networks, the Ibero-American Network of Health Experts in Rare Diseases (RIBERSER) and the International Collaboration on Rare Diseases and Orphan Drugs (ICORD) have demonstrated that no single institution or country can independently generate all the knowledge required for thousands of uncommon disorders. The need to combine worldwide policy with national and regional action plans was recognised early in the development of this field [4]. The published article summarised the Yukiwariso Declaration, adopted by the ICORD Board in 2011 and launched in Tokyo in 2012, which encouraged every country to establish rare-disease research and orphan-product development programmes with emphasis adjusted to its existing capabilities. International collaboration is therefore not an optional addition; it is a structural necessity.

Nevertheless, collaboration alone does not ensure that scientific progress reaches patients. Many global programmes are conceived within health systems possessing specialised centres, stable research financing, genomic infrastructure, trained personnel, interoperable data systems and regulatory mechanisms for orphan products. These conditions are not universally available. When strategies designed in well-resourced settings are transferred without adaptation, their technical quality may remain high while their practical relevance and accessibility diminish. The central argument of this article is that rare diseases present both intrinsic and extrinsic problems. The first are largely shared across borders; the second arise from national and local environments. Effective policy must distinguish them and connect international action with country-specific implementation.

The intrinsic problems of rare diseases

Intrinsic problems originate mainly in the nature of rarity itself. Small patient populations make natural-history studies, biomarker validation and adequately powered clinical trials difficult. Patients may be geographically dispersed, phenotypes heterogeneous and disease progression poorly characterised. Biological mechanisms may remain unknown, and appropriate cellular or animal models may not exist. Diagnostic expertise and validated tests are scarce for many disorders, while the economic return expected from conventional product development may be insufficient without dedicated incentives.

These problems do not respect national borders. A molecular mechanism discovered in one country, a natural-history cohort assembled in another and a therapeutic platform developed elsewhere can benefit the same international patient community. Shared ontologies, interoperable registries, biobanks, reference materials, common outcome measures and coordinated regulatory science reduce duplication and allow scarce cases and expertise to be aggregated. IRDiRC was created precisely to accelerate diagnosis and therapy through coordinated international research, and subsequent global initiatives have reinforced the importance of data sharing and cross-sector cooperation [5, 6].

The intrinsic dimension also explains why knowledge generated for one rare disease may have broader value. Platform technologies, drug repurposing, common trial designs, genomic interpretation tools and

methods for patient-reported outcomes can be reused across conditions. International collaboration is particularly efficient when it concentrates on these shared scientific and technological bottlenecks.

The extrinsic problems of rare diseases

Extrinsic problems are not determined primarily by a mutation, pathway or clinical phenotype. They arise from the environment in which the affected person seeks recognition and care. They include the organisation of the health system, geographical distribution of services, professional education, referral mechanisms, financing, regulation, social protection, availability of medicines, continuity of public policies and the capacity to produce and use health information [7].

The same disease can therefore lead to very different trajectories in different countries, provinces or socioeconomic groups. In one setting, a child with a complex phenotype may rapidly reach a multidisciplinary centre and receive genomic testing. In another, consultations may remain disconnected, records may not follow the patient and access to testing may depend on personal resources or judicial action. Even when an internationally accepted diagnosis exists, it may have limited practical value if confirmatory testing, genetic counselling, specialist follow-up or treatment is unavailable.

Comparative analyses of national rare-disease policies show considerable variation in their scope, governance, funding, implementation and responsiveness to patient needs [8, 9]. Latin America illustrates both growing political recognition and persistent differences among countries in legislation, institutional capacity, access and implementation [10, 11]. Comparable work in Africa has called for global action while documenting region-specific challenges and opportunities that require locally grounded policies, capacity building and multisectoral participation [12]. These disparities are not peripheral to the rare-disease problem. For many patients, they determine whether the condition is suspected, named, recorded, treated and socially recognised.

ICORD has sought to make these differences visible through annual meetings held in countries with diverse and, frequently, less-developed rare-disease ecosystems. By bringing international experience into direct dialogue with patients, clinicians, researchers, policymakers and other local stakeholders, these meetings help identify national needs that may be overlooked in programmes designed from a predominantly high-resource perspective. The ICORD 2024 meeting in Buenos Aires, for example, explicitly examined international models in relation to Latin American social, economic and health-system realities [13].

Extrinsic vulnerability also interacts with common health problems. A person with a rare disease still requires vaccination, nutrition, primary care, mental-health support, rehabilitation, dental care and management of common comorbidities. Safe treatment also requires pharmacovigilance systems capable of recognising and communicating risks in small, heterogeneous and frequently under-recorded populations [14]. When health services focus narrowly on the rare diagnosis—or when no diagnosis has yet been reached—preventable needs may be neglected. Environmental exposures, poverty, distance

from care and discontinuity of coverage can further amplify harm. Rare-disease policy should consequently be integrated with universal health coverage and with the ordinary responsibilities of national health systems, rather than constructed as an isolated, highly specialised enclave.

The invisible population without a confirmed diagnosis

Policies and registries commonly begin with a confirmed diagnostic label. This approach is administratively understandable but clinically incomplete. Many people live for years with unusual, severe or multisystem manifestations without receiving a definitive diagnosis. Others carry an incorrect or only provisional label. If eligibility for programmes, referral pathways and data collection depends exclusively on confirmation, the people facing the greatest diagnostic disadvantage may remain outside the system intended to assist them.

A recent global survey of undiagnosed rare diseases documented marked differences between countries in specialised centres, genomic technologies, national programmes and government policies. It concluded that targeted national strategies and aligned international cooperation are both necessary [15]. Experience from UDNI similarly shows the value of international exchange, but international networks work best when they reinforce local clinical systems capable of identifying cases, collecting phenotypic information, obtaining samples and providing continued care [16].

National rare-disease programmes should therefore recognise at least three operational groups: people with confirmed rare diseases; people with a clinically supported suspicion of a rare disease; and people with unexplained, atypical or multisystem conditions whose rarity has not yet been established. Registries need not merge these categories indiscriminately. They can use a layered approach with clearly differentiated levels of diagnostic certainty. This approach is essential in countries where confirmatory diagnosis is difficult because specialist expertise, validated testing, genomic technologies or financing are limited. If programmes count only confirmed cases, rare-disease problems may appear artificially small, become systematically underestimated or even be denied, producing a representation far removed from the true needs of affected people. A layered registry preserves data quality while also documenting unmet diagnostic need and the population that remains outside conventional disease-specific statistics. It should be conceived as a foundational instrument within a comprehensive national rare-disease plan—not as a substitute for that plan. The registry can reveal the scale and distribution of need, while the broader plan defines how the country will respond through referral pathways, diagnosis, integrated care, research, treatment access, financing and evaluation.

The same principle applies to disorders not primarily classified as rare skeletal, neurological, renal or metabolic diseases but which produce serious consequences in those systems. Severe osteopenia, deformity, loss of function or organ-specific complications may be clinically important even when they are secondary manifestations. Programmes organised in rigid diagnostic silos risk overlooking these cross-cutting needs.

Why global models require national adaptation

The choice is not between international standards and local adaptation. Both are required, but they serve different purposes. International standards make information comparable and allow knowledge to travel. National adaptation determines whether that knowledge can be used. A minimum data set may be shared internationally, for example, while additional variables reflect local ancestry, environmental exposures, diagnostic availability, social barriers or treatment pathways. A reference-centre model may define quality principles globally, while the number, distribution and functions of centres must reflect geography, population density, workforce and transportation.

The history of national plans in Europe also shows that formal adoption is only an initial step. Governance, measurable objectives, dedicated budgets, evaluation and renewal are needed if plans are to alter care [7]. A comparative review of eleven national policies found that countries addressed patient needs unevenly and that implementation could not be inferred merely from the existence of a policy document [8]. These lessons are highly relevant beyond Europe: importing the wording of a mature plan is easier than creating the institutions, financing and accountability that make it functional.

The World Health Assembly's recognition of rare diseases as a global priority creates a valuable opportunity. The emerging WHO global action plan is being developed through consultation with Member States and relevant stakeholders, while the WHO's supporting work highlights diagnostic delays, insufficient data, limited treatment access and the integration of rare diseases into universal health coverage [17, 18]. Recent contributions in *Journal of Rare Diseases* similarly frame rarity as an equity and health-system challenge and call for national plans, stronger data systems and context-appropriate implementation [19, 20]. This global framework should establish shared goals without obscuring different national starting points.

National priorities should be determined transparently. Prevalence and severity matter, but so do diagnostic feasibility, preventable harm, existing scientific strengths, capacity for regional cooperation, affordability and the possibility of building reusable infrastructure. For planning purposes, registries may stratify conditions by frequency—for example, relatively more prevalent rare diseases (approximately 1:2,000 to 1:20,000), an intermediate group, and ultra-rare diseases (below approximately 1:100,000)—provided these bands are treated as operational categories rather than universal definitions. Such stratification can help allocate expertise, diagnostic capacity and referral resources while preserving disease-specific information. Patient organisations contribute indispensable lived experience, but decision-making should also include clinicians, researchers, public-health authorities, payers, regulators and responsible industry participants. Conflicts of interest should be declared and managed rather than used to exclude entire sectors whose participation may be necessary for implementation.

From extrinsic barriers to measurable national responsibilities

A useful division of responsibilities is to place shared scientific challenges principally within international cooperation and implementation challenges principally within national or regional strategies. This is not an absolute separation. International partners can support capacity building, and national researchers contribute to global science. The distinction instead clarifies where accountability should lie.

International collaboration can provide disease definitions, ontologies, diagnostic algorithms, external quality assessment, research protocols, natural-history methods, ethical and data-governance principles, training, regulatory convergence and access to expert consultation. National programmes should map available services, establish referral pathways, identify gaps, create sustainable registries, finance essential diagnostics, support multidisciplinary care, determine locally appropriate reimbursement and connect patients with international resources. The core registry should be treated as national public-health infrastructure, with stable public financing and public accountability. Academic, philanthropic, patient-organisation or industry support may complement its development, but governance, access rules and continuity should not depend on a commercial sponsor or short-term project funding.

National plans should be evaluated against explicit indicators rather than the existence of a policy document alone. Relevant measures include diagnostic delay; the proportion of suspected cases reaching specialist assessment; geographic access outside major cities; coverage and completeness of the layered registry; movement of unresolved cases toward diagnosis; continuity of multidisciplinary care; access to indicated treatments; retention and training of professionals; locally initiated research; participation in multinational studies; and the proportion of agreed recommendations that are implemented. Targets should be adapted to national starting points and reported periodically so that progress, stagnation and regional inequalities become visible.

This approach is consistent with the experience discussed at ICORD 2024 in Buenos Aires, where international models were explicitly considered in relation to Latin American social, economic and health-system realities [13]. It also reflects the broader principle that global networks should reinforce—not substitute for—local medical systems.

Table 1
Division of responsibilities within an integrated rare disease strategy

Dimension	Intrinsic challenges	Extrinsic challenges
Primary arena	International and cross-border cooperation	Comprehensive national or regional plan
Core purpose	Generate and share scarce scientific knowledge	Convert knowledge into equitable access and care
Key instruments	Shared standards, data, expertise, platforms and multinational studies	Referral, financing, regulation, workforce, care networks and evaluation
Information base	Interoperable datasets and cross-border registries	Layered national registry of confirmed, suspected and unresolved cases, under public governance
Accountability	Collaborative outputs and globally reusable tools	Improved diagnosis, access, coverage, continuity, measurable outcomes and national capacity

The layered registry is an information and planning infrastructure within the comprehensive national plan; it is not an alternative to integrated policy and services.

Implications for low- and middle-income countries

The category of low- and middle-income countries is useful for drawing attention to settings in which rare-disease ecosystems may remain less developed, but it should not imply a single homogeneous group. National income classifications alone do not capture scientific capability, inequalities, political continuity or the organisation of care. Some middle-income countries have internationally recognised research groups and sophisticated urban centres while large parts of their populations lack consistent access to diagnosis and treatment.

These countries should not be viewed only as recipients of knowledge or sites for patient recruitment. They possess distinctive populations, clinical experience, scientific talent and opportunities for innovation. With appropriate incentives, local academia and small or medium-sized enterprises can develop diagnostics, repurpose medicines and generate affordable technologies responsive to regional needs. International partnerships should include equitable agenda setting, authorship, access to data, technology transfer, professional training and a credible route for benefits to return to participating communities.

Pragmatism is essential. A country may not immediately be able to finance comprehensive genomic testing or every high-cost therapy, but it can improve professional awareness, create referral rules, establish a minimum registry, connect clinicians with external experts, protect samples for future analysis and evaluate a limited number of high-impact interventions. Modest investments in organisation and information can prevent duplication and make later investments more effective.

Conclusions

Rare diseases require global science and local responsibility. Their intrinsic problems—scarce knowledge, small populations, methodological difficulty and limited incentives—make international collaboration indispensable. Their extrinsic problems—fragmented care, inequality, weak infrastructure, financial barriers and discontinuous policy—require national strategies adapted to real conditions, supported by public accountability and measurable objectives.

A successful global programme should therefore be universal in aspiration but flexible in implementation. It should define standards that allow countries to cooperate while helping each country build the minimum capacities needed to find, diagnose, care for and learn from its own patients. Most importantly, it should not restrict visibility and assistance to those fortunate enough to have obtained a confirmed diagnosis. People with suspected and undiagnosed rare conditions belong within the scope of rare-disease policy.

Recognising the intrinsic–extrinsic distinction does not divide the field. It provides a practical way to connect scientific ambition with health-system reality and to ensure that international progress becomes meaningful where patients actually live.

Abbreviations

ICORD

International Collaboration on Rare Diseases and Orphan Drugs

IRDiRC

International Rare Diseases Research Consortium

LMICs

low- and middle-income countries

RIBERSER

Ibero-American Network of Health Experts in Rare Diseases

UDNI

Undiagnosed Diseases Network International

WHO

World Health Organization.

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Consent for publication

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Availability of data and materials

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Author contributions

EJAR conceived the argument, developed the manuscript, reviewed the evidence and approved the final version.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the author used ChatGPT and Grammarly to improve its readability and language. Following the use of these tools, the author reviewed and edited the content as necessary and takes full responsibility for the content of the publication.

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