Editorial

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From system building to global engagement: Current significance of and future directions for rare disease research in China

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SUMMARY: Rare disease research is undergoing a gradual shift from a primary focus on single-disease mechanisms and drug development toward a more comprehensive agenda encompassing healthcare systems, policy frameworks, and patient engagement. The themed issue of *Intractable & Rare Diseases Research (IRDR)*, entitled "*Rare Diseases and Orphan Drugs in China: From System Building to Global Engagement*," systematically presents China's recent efforts in building governance structures for rare diseases, strengthening clinical collaboration networks, increasing the use of real-world data, and fostering multi-stakeholder participation. Emerging within the context of a large population and pronounced regional disparities, the Chinese experience offers new analytical perspectives and practical reference points for global rare disease research. It also contributes to an ongoing paradigm shift—from isolated, single-disease breakthroughs toward the development of sustainable, system-level capacity.

Keywords: rare diseases, strengthening of the healthcare system, real-world evidence, policy and governance, international collaboration

Rare disease research is currently at a critical historical juncture. Over the past several decades, the field has been largely led by Europe and North America, with a primary focus on gene discovery, precision diagnostics for individual diseases, and the development of orphan drugs. The advent of high-throughput sequencing technologies has accelerated advances in gene identification and the elucidation of genetic mechanisms (*1*). International collaborations, such as the International Rare Diseases Research Consortium (IRDiRC), have further galvanized global efforts to facilitate a molecular diagnosis of all rare genetic diseases (*2*). Together, these scientific achievements have established a solid foundation linking disease mechanisms to therapeutic targets and diagnostic pathways.

However, as rare disease therapies are increasingly used in clinical practice and become embedded within broader social systems, breakthroughs at the level of individual diseases alone are no longer sufficient to address the long-term and complex challenges encountered in real-world settings. Rare disease research has evolved into a cross-system, interdisciplinary endeavor, spanning biomedicine, healthcare policy, financing mechanisms, and patient engagement.

The themed issue of *Intractable & Rare Diseases Research*, entitled "*Rare Diseases and Orphan Drugs in China: System Building and Global Engagement*," aims to present China's multi-level efforts to rapidly construct a governance framework for rare diseases. By examining developments in institutional design, clinical collaboration, utilization of real-world data (RWD), and societal participation, this issue seeks to enrich the global academic understanding of rare disease research.

1. Divergent starting points and pathways: The heterogeneous landscape of global rare disease research

Europe and North America have amassed extensive experience in rare disease research and pharmaceutical incentive policies. Their approaches have primarily focused on leveraging legal frameworks and research incentives to stimulate drug development for rare conditions and to advance gene discovery (*3,4*). In parallel, Asian countries such as Japan have pursued long-term efforts to build systems grounded in universal health insurance and designated intractable disease programs that encompass disease definitions, clinical practice guidelines, and mechanisms for a structured follow-up (*5,6*).

The Chinese context is more complex. On the one hand, China has an exceptionally large patient population and substantial regional heterogeneity; on the other hand, system-level components—including patient registries,

policy formulation, clinical collaboration networks, and financing mechanisms—are still undergoing rapid development (*7,8*). In recent years, domestic research on the use of RWD, policy analysis, and multi-stakeholder collaboration has expanded, offering distinctive analytical perspectives and raising novel questions that are relevant not only to China but also to the global rare disease research community.

2. From "isolated breakthroughs" to "system-level capacity": Shared insights from this themed issue

The studies presented in this themed issue cover a diverse range of topics. In addition to clinical interventions and disease mechanisms, they examine system-level issues such as health technology assessment, reimbursement policies, and the obtaining of real-world evidence (RWE). Several shared insights emerge.

First, system-level capacity constitutes an indispensable component of rare disease research. The absence of robust patient registries, coordinated diagnostic and treatment networks, and coherent policy frameworks can directly constrain both scientific progress and clinical translation.

Second, RWD and RWE have become unavoidable foundations for research, particularly in the context of rare diseases, where limited sample sizes often render randomized controlled trials infeasible. A growing body of domestic and international research indicates that RWE is playing an increasingly important role in regulatory decision-making and health technology assessment, while also serving as a critical source of evidence that complements conventional clinical trials (*9,10*).

Third, multi-stakeholder collaboration is reshaping the research ecosystem. Changes in the modes of interaction among patient organizations, regulatory authorities, payers, and researchers are transforming the landscape of rare disease research and governance. This transformation is especially evident in the development of clinical pathways, policy decision-making processes, and the incorporation of patient-reported outcomes (PROs), where the value of collaborative approaches is becoming increasingly apparent.

3. Four forward-looking considerations

3.1. Formally integrating national and regional system building into the rare disease research agenda

Growing research and policy experience indicates that the presence of legal and institutional frameworks is a fundamental prerequisite for an effective, system-level response to rare diseases. Policy research should not be regarded as a peripheral concern, but rather as an integral component of rare disease research, on par with clinical and biomedical sciences.

3.2. Promoting diversification and contextualization of evidence pathways

RWE, health economics, and policy research can complement conventional clinical trials by providing a broader evidentiary base for assessing the value of rare disease therapies. Journals such as *The BMJ* and consensus statements have also proposed standardized reporting frameworks for the planning and reporting of RWE studies (*11*), offering guidance for improving the rigor and quality of such evidence.

3.3. Strengthening cross-system and cross-regional comparative research

Differences across countries in health insurance arrangements, regulatory frameworks, and social support systems provide valuable comparative perspectives for global rare disease governance. Asia, in particular, warrants closer examination, as its institutional contexts differ substantially from those of Europe and North America. Insights derived from these settings can inform global strategies and practices.

3.4. Recognizing the structural role of patients in rare disease science

The involvement of patient organizations in setting research priorities, generating data resources, and providing policy feedback has demonstrated tangible benefits in multiple countries. This trend contributes to the enhancement of the societal relevance, legitimacy, and credibility of rare disease research.

4. *Intractable & Rare Diseases Research* as an international platform and bridge for rare disease research

Intractable & Rare Diseases Research (IRDR) is committed to fostering an interdisciplinary platform for exchange that spans biomedicine, policy research, methodological innovation, and societal engagement. This themed issue serves not only as an initial presentation of the Chinese experience, but also as a reflection on—and an extension of—prevailing global paradigms in rare disease research. It underscores the need to articulate a more sustainable and impactful scientific agenda that integrates big data, RWE, policy systems, and patient participation.

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